Clinical Policies and Procedures

Purpose
To ensure safe and effective treatment of patients undergoing Botox® administration at a SpaMedica® medspa franchise or corporate store, the following policies and procedures have been developed.

Policy
A Registered Nurse [RN], or Physician Assistant with current state licensure shall be able to assess, consult and treat clients with Botox® following the guidelines set herein. In the state of California, the medical director or a physician assistant must perform a good faith examination prior to the use of Botox®.

(i) Setting
The Registered Nurse [RN], or Physician Assistant can perform the administration of Botox® in various settings and locations, such as but not limited to:

• All Botox® procedures must only be performed within the designated SpaMedica® medspa location that is registered with the Franchisor. All safety policies and procedures, as set out in the SpaMedica® Policy and Procedure manual, must be strictly adhered to.

All Botox® administration procedures shall be performed in a clean, safe environment, equipped with proper sharps disposal system, and universal precautions in place.

(ii) Supervision
The Registered Nurse [RN] or Physician Assistant shall function under the general supervision of the Medical Director who is immediately available for consultation by telecommunication and is physically available as medically necessary. The Medical Director is under contract with the SpaMedica® Medical group, which is a physician-owned company that hires doctors to act on behalf of SpaMedica® for an approved franchise. The SpaMedica® medical spa Franchisor will seek out potential SpaMedica® medical directors for the best medical care and medical supervision with a medspa facility.

Side effects may appear either at the time of treatment or shortly thereafter. Adverse reaction(s) shall be documented in the client’s SpaMedica® treatment record and the chart. All adverse reactions such as lid ptosis, diplopia, lower eyelid retraction, and weakening of the lacrimal pump shall be reported immediately to the Medical Director. Adverse reaction(s) shall be documented in the client’s chart.
(iii) **Patient Conditions**

The Registered Nurse [RN], or Physician Assistant will not knowingly treat any clients with:

1. Allergies to eggs, egg products, albumin,
2. Any clients with significant autoimmune or neurological diseases, or
3. Pregnant clients.

The Registered Nurse [RN], or Physician Assistant will only treat patients with Botox® after completing the SpaMedica® comprehensive Franchisee clinical training program and reviewed the sections in the clinical services manual dealing with the face and will not treat any portion of the face below mid-cheek areas.

**Botox® Procedure**

The Registered Nurse [RN], or Physician Assistant will:

1. Complete the SpaMedica® assessment and a medical history questionnaire with all new clients.

2. Clients with a history of allergies to human albumin, clients with significant neurological and autoimmune diseases, or pregnant clients will be denied treatment.

3. Upon passing medical screening, clients will be fully informed of risks, benefits, and potential adverse reactions, including the off label cosmetic use of Botox® for areas that extend beyond the frown lines of the forehead and a SpaMedica® informed consent will be signed.

4. Botox® shall be stored in a freezer [–5 degrees C or lower] until ready for use. Once reconstituted, it must be refrigerated [2–8 degrees C], not refrozen. Reconstituted Botox® should be clear, colorless and free of particulate matter.

5. Botox® shall only be reconstituted **just prior to use** and should be used within the first 4 hours according to the manufacturer. However, the SpaMedica® Medical Group feels that the Botox® can be refrigerated up to 30 days without any loss of efficacy. Gently rotate the vial and record the date and time of reconstitution on the SpaMedica® Botox® and injectable fillers.

6. **Vacuum will be released**, using a 21⁄22-gauge, 2.5 inch length-needle prior to reconstitution. If no vacuum is present the Botox® vial will be sent back to the manufacturer and a new vial shall be used following the same procedure.
7. Botox® should be reconstituted using 2.0 ml of preserved or non-preserved saline [0.9%] as a diluent, resulting in a 2.5 – 3.3 units per 0.1 cc. A 3–5 cc syringe containing non-preserved saline is attached to the ½ gauge needle [at a 45° angle] and SLOWLY injected into the vial. Allow the saline to flow down the sides of the vial, thus minimizing air bubble formation and not damaging the delicate Botox®.

8. Botox® is gently drawn up into a 1 ml tuberculin syringe using a ½ gauge needle. The injection is to be administered with a 30-gauge [½ inch] needle.

9. Clients are injected while in a seated position.

10. Clients are asked to demonstrate dynamically the function of the muscle groups to be injected.

11. Prior to administration the Registered Nurse [RN], or Physician Assistant will map out points of injection according to landmarks and location of muscle belly. The only areas of administration will be the corrugator, procerus, frontalis, and orbicularis oculi muscles in the forehead and periorbital region in the upper face. Mid-facial application. [Corrugator and procerus muscles for frown lines, frontalis muscle for horizontal forehead lines, and orbicularis oculi muscle for crow’s feet.] Midfacial Botox® may be added for lifting of the corners of the mouth (Depressor angularis oris,) Vertical lip lines (orbicularis oris), elevation of the tip of the nose (depressor septi Nasi muscle) smoothening of dimpled chin skin (mentalis) and softening of neck Cords (platysma).

Note: increased toxin dose may be necessary in older and male clients.

12. In an effort to reduce the complications of ptosis the following steps should be adhered to:
   a. Administer at least 1 cm above the central eyebrow and 1.5 cm–2 cm from the lateral canthus.
   b. Ensure the injected volume/dose is accurate and kept to a minimum.
   c. Avoid injection near the levator superioris, particularly in patients with larger brows.
   d. Medial corrugator injections should be placed 1 cm above the bony supraorbital ridge.

If mild lid ptosis should occur the nurse will instruct the client that this will resolve within a few weeks and in the use of [over the counter] Vasocon to assist in alleviating the ptosis. Ptosis or any other complications shall be immediately reported to the Medical Director and documented in the SpaMedica® client record.

1. Allergan recommends using 2.5 ml of non-preserved saline resulting in 4.0 units per 0.1 cc. However the accepted industry practice is as stated.

2. The RN shall be familiar with all general adverse reactions that can be associated with the administration of Botox® Cosmetic [Botulinum Toxin Type A]. Refer to Allergan Inc., publication, page 3, “Adverse Reactions – General” enclosed with each vial of product.
13. Syringe is inserted perpendicular to the skin and completed at a depth just beneath the dermis, 2.5 units to 5 units of Botox® is injected into each site.

14. After each injection the skin may be massaged moderately and pressure held with a gauze.

15. When procedure is completed the client will be educated to perform the dynamic facial expressions for the next hour, not to rub or manipulate the injection sites, not to lie down for a period of 4 hours, and to report any problems or complications to the clinic immediately.

16. Typically, the initial doses of reconstituted Botox® induce chemical denervation of the injected muscles 3 to 5 days after procedure, increasing in intensity during the first week.

(iv) Record Keeping

The Registered Nurse [RN], or Physician Assistant shall be responsible for maintaining client SpaMedica® Botox® treatment records, including but not limited to client assessment, signed informed consent of risks, benefits, and potential adverse effects, number of treatments, treatment sites, number of injections, solution/concentration used, and the client response to treatment.

Requirements for Clinical Personnel

(v) Training / Education

The Registered Nurse [RN], or Physician Assistant must complete the SpaMedica® franchisee certification and clinical training program. The SpaMedica® Medical Director, either a Medical Doctor, Doctor of Osteopathy, must also have completed the franchisee binder. Advanced Practice Nurses experienced in this procedure, or a teaching institution specializing in this procedure, may perform this training and certification. Competencies to successfully demonstrate shall include:

• Mechanism of Action of Botox®
• Basic Theory of Treatment for Cosmetic Purposes
• Facial Anatomy
• Storage, preparation, and dilution of Botulinum Toxin A
• Safety, efficacy, and complication issues
• Assessment and identification of areas to be treated
• Safe application of injection techniques [minimum 8 hours hands on training]
• Complications and their management
(v) Competencies & Documentation

The Medical Director, Registered Nurse and/or Physicians assistant shall:

• Document [on the appropriate form] the initial evaluation and final determination recording satisfactory completion of training and competence.

• Evaluate the competence of the Registered Nurse [RN], Physician Assistant or licensed medical personnel on an annual basis and/or as needed if indicated by client dissatisfaction or efficacy issues.

• The evaluation shall be maintained in the personnel file of the Registered Nurse, Physician Assistant or licensed medical personnel at the appropriate administrative office [employing facility].

Development and Approval of Standardized Procedure

The SpaMedica® Clinical Policies and Procedures for the Administration of Botox® have been developed jointly by the Medical Director, Administrator, Advanced Practice Nurse and/or Registered Nurse. This procedure shall be reviewed on an annual basis and documentation pertinent to that review shall be kept on file in the designated administrative office.

Signatures of authorized personnel approving the standardized procedure:

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<tr>
<th>Nurse</th>
<th>Date</th>
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<tr>
<td>Medical Director</td>
<td>Date</td>
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<tr>
<td>Administrator</td>
<td>Date</td>
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</table>
Personnel Authorized to Perform Procedure

Name | Date
--- | ---
1. | 
2. | 
3. | 
4. | 
5. | 

Botox® Post Treatment Instructions

- Avoid lying down for several hours following treatment.
- Facial exercise in the area of treatment is recommended [frown/smile 1 hour].
- Avoid manipulation of the area for the first four hours after procedure.

**Note:** These measures should minimize the possibility of ptosis.

- Treatment effect may take 3–8 days to appear.
- **The benefits may last 3–6 months, the average is 4 months.**
- A touch-up may be necessary in 1–2 weeks.
- Contact the practitioner as soon as possible after the eighth [8th] day if you have not achieved the desired effect.
DESCRIPTION: BOTOX COSMETIC® (Botulinum Toxin Type A For Injection) is a sterile, vacuum-dried form of purified botulinum neurotoxin type A complex, produced from a culture of the Hal strain of Clostridium botulinum grown in a medium containing N-Z amine, glucose and yeast extract. It is purified from the culture solution by a series of acid precipitations to a crystalline complex consisting of the neurotoxin, a non-toxic protein and four major hagglutinin proteins. The crystalline complex (average molecular weight of 500,000 Kd) is re-dissolved in saline solution containing albumin (human) and is sterile filtered (0.2 microns) prior to vacuum-drying. BOTOX COSMETIC® is to be reconstituted with unpreserved sterile saline prior to intramuscular injection.

Each vial of BOTOX COSMETIC® contains 100 units (U) of Clostridium botulinum toxin type A, 0.5 milligrams of albumin (human), and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative. One unit (U) corresponds to the calculated median lethal dose (LD50) in mice used reconstituted BOTOX COSMETIC® and injected intraperitoneally.

One unit (U) of BOTOX COSMETIC® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. The method utilized for performing the assay is specific to Ageron's proprietary assay method for mouse LD50 assays. Units of biological activity of BOTOX COSMETIC® can be compared to mouse LD50 units of any other botulinum toxin or any toxin assayed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxins are independent of animal test activity relationships to human test estimates. The specific activity of BOTOX COSMETIC® is approximately 20 units/gram of neurotoxin protein complex.

CLINICAL PHARMACOLOGY: BOTOX COSMETIC® (Botulinum Toxin Type A For Injection) blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BOTOX COSMETIC® produces partial chemical denervation of the muscle resulting in localized muscle paralysis. When chemically denervated, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus reversing muscle weakness produced by local injection of BOTOX COSMETIC®. In clinical studies involving patients with moderate-to-severe glabellar lines at maximum frown, BOTOX COSMETIC® injections significantly reduced the severity of the glabellar lines for up to 120 days, as measured by investigator rating of glabellar line severity at maximum frown and at rest, and by subject's global assessment of change in appearance of glabellar lines. Thirty days after injection, 84% of BOTOX COSMETIC®-treated patients were considered by investigators as treatment responders (none or mild severity at maximum frown), and 90% of patients felt they had moderate or better improvement, compared to 0% of placebo-treated patients.

INDICATIONS AND CLINICAL USE: BOTOX COSMETIC® (Botulinum Toxin Type A For Injection) is indicated for the treatment of glabellar lines associated with corrugator and/or procerus muscle activity.

CONTRAINdications: BOTOX COSMETIC® (Botulinum Toxin Type A For Injection) is contraindicated in patients with myasthenia gravis or Eaton Lambert Syndrome. BOTOX COSMETIC® is contraindicated in the presence of injection at the proposed injection sites.

BOTOX COSMETIC® is contraindicated in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS: The recommended dosages and frequencies of administration for BOTOX COSMETIC® (Botulinum Toxin Type A For Injection) should not be exceeded.

The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other drugs that interfere with neuromuscular transmission (e.g., toboconazole-type muscle relaxants). Caution should be exercised when BOTOX COSMETIC® is used with aminoglycosides, e.g., streptomycin, tobramycin, neomycin, gentamicin, netilmicin, kanamycin, amikacin, spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs that interfere with neuromuscular transmission. Caution should also be exercised when BOTOX COSMETIC® is utilized in disorders that produce a depletion of acetylcholine, in patients with amyotrophic lateral sclerosis, or disorders that produce peripheral neuromuscular dysfunction.

PRECAUTIONS: General: The safe and effective use of BOTOX COSMETIC® (Botulinum Toxin Type A For Injection) depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration technique.

In order to reduce the complications of ptosis, avoid injection near the levator palpebrae superioris, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the brow superorbital ridge.

As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.

Over the course of the double-blind and open-label studies, 120 subjects who had received three or more consecutive injections of 20 U of BOTOX COSMETIC® at four month intervals had serum antibody samples before and after each injection and four months after the third injection. Four of these subjects had a positive antibody result at one time-point during the study. None of these subjects had a positive antibody result from the blood sample taken four months after the third consecutive injection. The results of these tests are highly dependent on the sensitivity and specificity of the assay, and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. Treatment with BOTOX COSMETIC® for cosmetic purposes may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments with BOTOX for other purposes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX COSMETIC®. BOTOX COSMETIC® was not mutagenic in the in vitro and in vivo mutagenicity studies. A fertility and reproductive toxicity study following intramuscular injection of BOTOX in rats indicated the "no observable effect level" (NOEL) on reproduction was at dosages of 4 U/kg in male rats and at dosages of 6 U/kg in female rats. Pregnancy: Teratogenic Effects: The teratogenic effects of BOTOX® were evaluated in mice, rats and rabbits. No teratogenic effects were observed when pregnant mice were injected intramuscularly with doses of 4 U/kg (approximately 2/3 of the maximum recommended human dose) and 8 U/kg on days 5 and 13 of gestation; however, dosages of 16 U/kg induced a slightly lower fetal body weight. No teratogenic effects were observed in rats when injected intramuscularly with doses of 16 U/kg on days 6 and 13 of gestation, and 2 U/kg/day on days 6 through 15 of gestation. In rabbits, daily injections at dosages of 0.5 U/kg/day (days 6 through 18 of gestation) and 4 and 6 U/kg (days 6 and 13 of gestation) caused death and abortions among surviving animals. At lower doses (0.125 U/kg/day and at 2 U/kg/day), external malformations were observed in one fetus per dose. The rabbit appears to be a more sensitive species to BOTOX®.

Reproductive and Developmental Effects: The reproductive and developmental effects of BOTOX® were evaluated in rats at dose levels of 4, 8, 16 and 16 U/kg. Muscle atrophy at the injected site, reduced body weight gains and reduced absolute food consumption were observed following intramuscular injection of BOTOX® at doses of 4 U/kg and higher on days 5 and 13 of presumed gestation, and day 7 of lactation. No effects on maternal reproductive performance were observed at the highest dose tested, 16 U/kg (approximately three times the maximum recommended human dose). No adverse effects on development of the pups was observed at 4 U/kg, however, higher dosages were associated with reduced pup body weight and pup viability at birth.

There are no adequate and well-controlled studies of BOTOX® administration in pregnant women. Because animal reproduction studies are not always predictive of human response, BOTOX® administration is not recommended during pregnancy. If this drug is used during pregnancy while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations, which have been observed in rabbits.

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.

Information to be Provided to the Patient: Patients or caregivers should be advised to seek immediate medical consultation if swallowing, speech, or respiratory disorders arise.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations, which have been observed in rabbits.

ADVERSE REACTIONS: General: In general, adverse events occur within the first week following injection of BOTOX COSMETIC® (Botulinum Toxin Type A For Injection), and are transient. As is expected for any intramuscular injection procedure, localized pain, tenderness and/or bruising may be associated with the injection. Local weakness represents the expected pharmacological action of botulinum toxin.
Safety was evaluated in two multicenter, double-blind, placebo-controlled, parallel-group studies of identical design (N=553; 405 in the BOTOX COSMETIC®-treated group and 130 in the placebo-treated group). The most frequently reported treatment-related adverse events were headache (9.4% in the BOTOX COSMETIC®-treated group and 15.4% in the placebo-treated group) and blepharoptosis (3.2% in the BOTOX COSMETIC®-treated group and 0% in the placebo-treated group). Blepharoptosis is consistent with the pharmacologic action of BOTOX COSMETIC®, and may be technique related.

Adverse events that were reported as treatment-related and were reported in 1-3% of BOTOX COSMETIC®-treated patients are listed in decreasing order of incidence: injection site pain/bruising/redness (2.5%), pain on injection (2%), erythema (1.7%), local muscle weakness (1.7%), injection site ecema (1.3%), dysphagia (1%), skin tightness (1%), ptosis (1%) and nausea (1%). Most adverse events reported were of mild-to-moderate severity and all were transient.

In a multicenter, open-label, repeat injection study, 318 patients who had participated in one of the two double-blind studies and who had glabellar line severity of at least mild severity at maximum frown received 2 additional treatments of BOTOX COSMETIC®. In this study, adverse events were comparable in type, incidence, severity, and causality to those reported in the two placebo-controlled, double-blind studies.

The following events have been reported rarely (<0.1%) since BOTOX® has been marketed: skin rash (including erythema multiforme, urticaria, and pruritis- forme eruption), pustule, allergic reaction, and facial paralysis.

In the treatment of other indications with botulinum toxin type A, there have been rare spontaneous reports of death, sometimes associated with 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 cardiovascular disease.

OVERDOSE: In the event of overdose or injection error, additional information may be obtained by contacting Allergan, Inc. at (800) 433-8871.

No cases of systemic toxicity have been reported following accidental injection or oral ingestion of BOTOX® (Botulinum Toxin Type A for Injection). Should accidental overdose occur, the patient should be monitored for approximately one week for signs or symptoms of systemic weakness or muscle paralysis.

Patients with botulism may present with symptoms of ptosis, diplopia, weakness of the neck, ribs, cranial nerve findings, generalized weakness, or paresis of the respiratory muscles. Overdose of BOTOX COSMETIC® is a relative term and depends upon dose, site of injection, and underlying tissue properties. Local weakness is usually well tolerated and resolves spontaneously without intervention. However, dysphagia may result in loss of airway protection and aspiration pneumonia.

DOSE AND ADMINISTRATION: For Intramuscular Use Only

The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative. Do not freeze reconstituted BOTOX COSMETIC® (Botulinum Toxin Type A for Injection). Once opened and reconstituted, use within four hours and discard remaining solution.

BOTOX COSMETIC® is reconstituted with 0.9% sterile non-preserved saline (100 units in 2.5 mL or injected as 4 U/0.1 mL). 0.1 mL (4 U) should be administered using a 30 gauge needle in each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 U.

In order to reduce the complication of ptosis, injection near the levator palpabrae superiors should be avoided, particularly in patients with larger brow-depressor complex. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

An injection of BOTOX COSMETIC® is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin (see Dilution Table) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe may be attached to the electromyographic injection needle, preferably a 1.5 inch, 27 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX COSMETIC®.

Lack of Response: There are several potential explanations for a lack or diminished response to an individual treatment with BOTOX COSMETIC®. These may include inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders, change in pattern of muscle involvement, patient perception of benefit compared with initial results, inappropriate storage or reconstitution, as well as neutralizing antibodies to botulinum toxin. A neutralizing antibody is defined as an antibody that inactivates the biological activity of the toxin. However, there were patients who continued to respond to therapy and demonstrated presence of neutralizing antibodies; the proportion of patients which lose their response to botulinum toxin therapy and have demonstrable levels of neutralizing antibodies is small.

The critical factors for neutralizing antibody production are the frequency and dose of injection. To reduce the potential for neutralizing antibody formation, it is recommended that injection intervals of BOTOX COSMETIC® should be no more frequent than two months. More frequent injections should not be required, as BOTOX COSMETIC® treatment reduces the severity of the glabellar lines for up to 120 days.

A suggested course of action when patients do not respond to BOTOX COSMETIC® injections is: 1) wait the usual treatment interval; 2) consider reasons for lack of response listed above; 3) more than one treatment should be considered before classification of a patient as a non-responder; 4) test patient serum for neutralizing antibody presence.

RECONSTITUTED SOLUTIONS: To reconstitute vacuum-dried BOTOX COSMETIC®, use sterile normal saline without a preservative: 0.9% Sodium Chloride Injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since BOTOX COSMETIC® is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX COSMETIC® should be administered within four hours after reconstitution.

During this time period, reconstituted BOTOX COSMETIC® should be stored in a refrigerator (2° to 8° C). Reconstituted BOTOX COSMETIC® should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

Dilution Table

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<th>Diluent Aced</th>
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<tr>
<td>2.5 mL</td>
<td>4.0 U</td>
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SPECIAL INSTRUCTIONS: All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

STORAGE: Store the vacuum-dried product either in a refrigerator at 2° to 8° C, or in a freeze at or below –5°C. Administer BOTOX COSMETIC® within four hours after the vial is reconstituted. During the four hours, reconstituted BOTOX COSMETIC® should be stored in a refrigerator (2° to 8° C). Reconstituted BOTOX COSMETIC® should be clear, colorless and free of particulate matter.

HOW SUPPLIED: Each vial contains 100 U of vacuum-dried Clostridium botulinum toxin type A.

Product Monograph available on request.

April 2003

ALLERGAN Inc.

Markham, Ontario, Canada, L3R 9S1

717111EC10M
What is Botox Cosmetic™?
Botox Cosmetic™ is a treatment for wrinkles such as crow’s feet, frown lines and the furrow in your brow.
You know what would help you out – is a proper consultation here in our office – why don’t we book one for you?
All of your questions will be fully answered!

Is it safe?
Yes! Botox® has been available for 20 years and has been used to treat many diseases (including cerebral palsy) and has been proven to be very safe through extensive testing and research.
Botox Cosmetic™ is an approved drug used to treat patients for cosmetic wrinkles.
Why don’t we book a consultation for you so that all of your questions can be answered?

Will it give me food poisoning/Is it botulism?
No – Botox Cosmetic™ is NOT botulism and it will not cause food poisoning. To clarify for you, Botulism is the name of an illness.
The product is a natural, purified protein. It is an approved prescription drug that is used in tiny doses.
It comes from a naturally occuring bacteria and it is purified in a lab – similar to how Penicillin comes from mould!
Why don’t we book a personal consultation for you so that all of your questions can be answered?

Isn’t Botox Cosmetic™ a toxin/poison?
No, it is not a poison! No, it is not toxic to you!
Botox Cosmetic™ is a natural, purified protein. It is an approved drug that is used in tiny doses.
It comes from a naturally occuring bacteria – similar to how Penicillin comes from mould!
Why don’t we book a consultation for you so that all your questions can be answered?

How do I know it won’t be toxic for me?
Typically, for a cosmetic treatment, you may receive under 100 units.
Botox Cosmetic™ would only be toxic to you if you received over 3,500 units all at one time. You really are getting very tiny doses.
Why don’t we book a consultation for you so that all your questions can be answered?
**How does it work?**

Botox Cosmetic™ works by relaxing the muscles underneath the skin to create a smooth and refreshed appearance.

Why don’t we book a consultation for you where you can ask all of your questions? (When asked in office, bring to front desk to book a consultation.)

**How long does the procedure take?**

Generally, after the consultation, the procedure only takes up to 15 minutes.

Since there is no downtime – you can do it on your lunchtime!

Why don’t we book a consultation for you?

**How quickly does it work?**

It can take up to 2 weeks for it to take full effect.

Why don’t we book a consultation for you?

**My treatment didn’t work!**

Botox Cosmetic™ takes up to 14 days to take full effect. When was your treatment done?

If LESS than 2 weeks ago, say to patient:

You will need to wait until the full 2 weeks has passed and then please call us if you have any concerns.

If MORE than 2 weeks ago, say to patient:

Okay, then let’s book an appointment with the Doctor so that you can be re-assessed and to see if you require a little more product. Are you available on ________________?

**How long does Botox Cosmetic™ last?**

No – Botox Cosmetic™ is not permanent. It lasts between 3–4 months on average but everyone is different.

Why don’t we book a consultation for you?

**How is it done?**

It is injected with a very tiny needle (it only feels like a little pinch).

Why don’t we book a consultation for you?
Does it hurt?
Most patients say the injections feel similar to a little pinch, although everyone is different.
I usually hear that patients say, “Is that all?”
Why don’t we book a consultation for you?

How much does it cost?
The cost of treatment varies by each patient and a personal consultation can give you a specific amount.
The cost can range from $300 and up. There are a few things you should consider in addition to price:

- Medical Licence of physician
- Years of experience of physician
- We have treated hundreds of patients here who keep returning

The doctor is wonderful!
Why don’t we book a consultation for you so that you can get a specific amount?
If patient persists on cost per unit:

Our clinic charges $________/unit but the details of what it may cost for you needs to be discussed with the doctor.

What about the cost/experience of the injector (Why should I come to you?)
Dr. XXXXXXX has been specializing in dermatology/plastic surgery since 19XX. He is Board Certified in Canada and is a member of the XXXXXXX Society of Physicians.

Why don’t we book a consultation for you so that you can meet him and get more information?

What is a unit?
A unit of Botox Cosmetic™ is simply a very tiny measurement of drug.
The number of units you require (to achieve the look you want) needs to be discussed with the doctor during the consultation.

Why don’t we book a consultation for you so that you can discuss this in more detail with him?
I don’t want to look like a mask without expression – will that happen?
No. We ensure you get the look you want – as natural as you want.
Everyone wants a different look and we strive to make you happy!
Why don’t we book a consultation for you so that all your questions can be answered?

What are the side effects?
Side effects are rare and are not permanent.
There can be some minor bruising (which is easily covered up with makeup) or a slight headache.
Why don’t we book a consultation for you where all the details can be discussed?

I have heard that you can get a drooping eyelid – is this true?
Side effects are rare and are not permanent and this can include a drooping eyelid.
The incidence of these side effects are less than 1%.
Why don’t we book a consultation for you where you can ask all of your questions?

Where does it go in my body?
Botox Cosmetic™ stays local to the muscle where it is injected.
Why don’t we book a consultation for you where you can get more detailed information from the doctor?
If the patient wants more information, you can answer with:

“After the injection Botox Cosmetic™ is simply metabolized and broken down into natural by-products.”

I have (any medical condition). Can I get Botox Cosmetic™?
That is a great question! However, I am not a physician and therefore, that can only be answered during a private consultation with Dr. XXXXX.

Why don’t we book an appointment for you so that all your questions can be answered?

What to do when a patient wants to keep asking you detailed questions about a procedure on the phone:
Since you are asking a lot of great questions, I recommend that you write down all your questions on a piece of paper. We should book a personal consultation for you... you can bring your list and ensure that nothing is overlooked!
It has been a pleasure speaking with you and answering some of your questions. However, I must excuse myself. Our patient coordinators are better able to answer your questions.

We have an opening on ________________.

*How to explain the consultation process and try to minimize no shows.*

I’d like to tell you about your consultation so that you know what to expect:

We book a dedicated appointment with you and one of our highly qualified staff. This can be done with one of our highly trained patient coordinators or with the doctor.

You have the entire time to ask questions, discuss your individual concerns and expectations.

If you feel comfortable, we have also included special time for you to have the treatment done during the appointment, although you are not obligated.

We will call to confirm your appointment, BUT since we have set aside dedicated time to meet with you, it is very important that you let us know if you cannot make your appointment.

*Some industry data*

2002 global survey on “Public Perceptions and Attitudes Towards Facial Appearance”

- 80% of Canadians consider physical attractiveness *somewhat to very important* in today’s society
- 67% of Canadians want their face to look young for their age.
- 35% of Canadians agree that there are things about their face that they would like to change.
- 78% of women under 45 consider using various treatments and procedures to improve their appearance.
- 63% of Canadians would go to their doctors (dermatologists, plastic surgeons or family/general physicians) as their main source of information about facial treatments or procedures

*The Botox Cosmetic™ Boom*

- Botox Cosmetic™ is the most common and fastest growing cosmetic procedure performed in North America
- More than 100,000 Botox injections on 50,000 patients in 2003 in Canada
- 325% increase in number of practices offering non-surgical procedures
- 1 in 2 Canadians have heard about Botox Cosmetic™
- 75% of the core target have heard about Botox Cosmetic™
Consumer Perceptions of Treatment Options

- Surgery
- Injectables
- Superficial
  - removing unwanted blemishes/hair
  - peels/facials
- Lotions & Potions

Larger mental step for many consumers from superficial to injectables.

Rethinking the Business Model

Turning the Business Upside Down

Medical/Surgical Practice | Cash pay practice
Doctor | High control | Staff
Staff
Patient | Low Control | Doctor

What is Marketing?

Comprises everything that expresses who you are and what it is that you do

- Is how you make others aware of your offerings
- Is your relationship and credibility with your prospects and customers
- It creates the perception of value people have of your clinic

Four Pillars of Marketing

- An “outside-in” perspective:
- Target market
  - Customer needs
  - Integrated marketing
  - Profitability

Target Market

- Who is the target market?
- How big is the target market?
- What are the needs of the target market?
**Botox Cosmetic™ Market Potential**

**TARGET MARKET**
- W35–54
- HHI>60K
- Self-esteem mindset
  (PMB data)
- 2,000,000 people

% consider elective non-surgical cosmetic procedures
(CMR Dec 02)
- 11%

Accessible Canadian Market
- 220,000 People

**Today’s Botox Cosmetic™ Customer**

- See Botox treatment as part of general self-enhancement rather than a solution.
- Wrinkles/lines not seen in isolation.
- Needs to be informed of benefits
- Barriers to use largely attributed to:
  - Lack of information including negative and incorrect information
  - Fear/safety concerns
  - Low familiarity

**Integrated Marketing**

- Receptionist, Esthetician, Nurse, Patient Coordinator, Medical Staff work together to serve the customer’s interests
  - Accepts responsibility for providing timely patient service in a courteous manner.
  - Understands that the success of the practice depends on good service
  - Learns and practices patient service in a positive manner.
Customer Cascade

POTENTIAL CUSTOMERS
Marketing drives potential customers to

CALL YOUR PRACTICE
Front line staff convert calls into

CONSULTS
Uncovering needs convert consults into

PATIENTS
Customer satisfaction drives

REFERRALS! – Easier to convert and retain a referral customer than a new one.

EVERYONE MUST “THINK CUSTOMER!”

Why is it important to satisfy target customers?

PROFITABILITY
• Revenues come from two distinct groups:
  – New customers
  – Repeat customers
• How much does it cost to attract new customers vs. keeping existing customers happy?

6–10 TIMES THE COST OF AN EXISTING CUSTOMER

PEOPLE USUALLY MAKE UP THEIR MINDS ABOUT SOMEONE IN 10 SECONDS OR LESS!

Incredible Customer Service
• Attitude: Smiling & Eye Contact
• Energy: Upbeat & Positive
• Appearance: Professional

“opinions are established within 90 seconds of the patient entering the practice and meeting the staff”

Positive Telephone Image
75% to 90% of patients’ first contact with the practice is by telephone.

68% of patients who decided to seek care elsewhere did so because of staff discourtesy/rudeness.
A Few Simple Telephone Tips

- Answer phone by the third ring
- Have phone answered over the lunch hour
- Ensure enough phone lines to manage call volume at peak periods
- Answer phone in friendly tone (SMILE) with name of practice and your name
- Ask if you can put a person on hold
- When transferring calls inform both the customer and your colleague of the important details.

What is your ultimate goal?

What else should you tell your patients during that 1st call?

- Are you thanking your patients for their interest in your practice?
- Are you telling your patients how to get to your practice – exactly?
- Where is parking, public transportation (costs)?
- What to expect when they arrive?
- Anything else specific to your practice to help your patients get to you and to keep their appointment?

Top 10 Tips to Retain More Patients

1. Provide consistently great service.
2. Under promise and over deliver.
3. ALWAYS book a 2 week follow-up.
4. ALWAYS take before & after photos.
5. ALWAYS be proactive about booking the next treatment date!!!!!
6. Personalize your interaction with the patient.
7. Cross sell all your services – don’t be afraid to make suggestions.
8. Maintain a wait list (be proactive).
9. Calculate your retention rates.
10. Set goals to improve retention.
Botox Cosmetic™ Benchmarking Database Survey Results

- Canadian Cosmetic Practices largely failing to capture current potential, (28% net conversion) although there has been improvement
- Telephone Conversion Rates: 20% to 60%
- Counseling Conversion Rates: 65% to 95%
- Repeat treatment rates: 40% to 80%
- Tap into the power of “Creating Patient Advocates”

What this all means

<table>
<thead>
<tr>
<th></th>
<th>Dr. Average</th>
<th>Dr. Good</th>
<th>Dr. Best</th>
</tr>
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<tbody>
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<tr>
<td>Number of consults</td>
<td>24 (40%)</td>
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<td>48 (60%)</td>
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<td>Rate of procedure</td>
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<td>$500</td>
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<tr>
<td>Revenue</td>
<td>$8,500</td>
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<td>$23,000</td>
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<tr>
<td>Retention (Repeat)</td>
<td>18 (40%)</td>
<td>37 (80%)</td>
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</tr>
<tr>
<td>Total Revenue</td>
<td>$32,000</td>
<td>$41,500</td>
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In Summary...

Make sure the image of the practice is reflected in everything that you do

- Provide easy access to the practice via the phone, e-mail or Internet
- Make communication easy for your customers and focus on their needs – LISTEN
- Build rapport quickly to develop a strong relationship
- Always put the customer first
Consultation Process

Botox®

1. Client must complete a Medical/Surgical History, review and sign Payment Policy, review and initial pages of Botox® Consent Form. A good candidate for Botox® would be individuals with expression lines or facial wrinkles that persist despite other treatments.

2. Review history with client in consultation. Consent is reviewed as well until client has no further questions.

3. Explain indications for Botox® such as glabellar lines, horizontal brow lines, crow’s feet, lower lid roll, bunny lines on the side of the nose, lips, chin, mandible, and neck bands. A good candidate, as stated above has had a thorough discussion of product description, risks, benefits, post care and longevity (which can be up to 6 months). This is also a good time to discuss all other services that SpaMedica® offers. Information pages are available on all procedures.

4. Be sure client is aware of post treatment instructions, and that they have a post care page to take home with them. It includes the clinic phone number on the bottom of the page if they have any concerns.

5. Discuss all issues regarding injection technique so the client is aware of our Num It cream; our cryo cooler is also available.

6. All pages of consent must be initialed, the last page to be filled out by injectable nurse as to specific area of injection. Have client sign the bottom of this page and the nurse will witness with her signature.

7. Photos are taken with the Polaroid camera, usually kept in treatment room one. Photos are labeled and kept in the patient’s chart in envelopes that will stick in the front of the chart. These are kept at the front desk.

Medical/Surgical History

Patient Name: ___________________________ I.D. # __________________

In this time of rapidly expanding medical knowledge and the increasing specialization associated therewith, there exists a very real risk of the specialist physician not being aware of the general health and medical background of the patient. On occasion such information may critically affect what procedures we may safely undertake on you and under what circumstances. We therefore ask that you give us the following medical information.

Age: _____ Height: _____ Weight: ______ Occupation: _______________________

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<th>Medication(s):</th>
<th>Amount</th>
<th>Frequency</th>
</tr>
</thead>
</table>

Please list all medications which you are currently taking or have used in the past 6 months (be sure to include any of the following: birth control pills, aspirin or ibuprofen containing drugs, Phen-Fen, Redux, diabetic medications, steroids, glaucoma drops, asthma medications, Digoxin, Lanoxin, nitroglycerin, Isordil, Inderal, other heart medications, Lasix, other diuretics, high blood pressure medications, Coumadin, Persantine, tranquilizers, sleeping pills, anti-depressants, pain pills or injections, epilepsy medications). Use back of page if necessary.

Please list all Naturopathic or Health Food Supplements:

List all drug and/or latex allergies:

Have you ever used (circle): LSD/speed/cocaine/marijuana?

If yes, when did you last use ____________________________________________

Are you a smoker? YES/NO _____ Ex-Smoker YES/NO _____ Non-Smoker YES/NO _______

How much are (were) you smoking? ______ How long? ______ Quit how long ago? _______

How much alcohol do you drink? _______________________ Caffeine? _____________
Please circle all of the following medical conditions you now have or have had in the past:

bleeding tendency / diabetes / blood transfusions / glaucoma / dry eyes / lung disease /
TB / asthma or wheezing / emphysema / bronchitis / irregular heart beat / chest pain /
heart disease / high blood pressure / heart attack / stroke / epilepsy / heart burn / intestinal
ulcers or bleeding / rheumatoid arthritis / scleroderma / lupus / depression / mental illness /
drug or alcohol addiction / hepatitis B / hepatitis C / HIV / any other serious illness or injury /
None of the above

Is there any possibility that you may be pregnant at this time? YES/NO _______________________

Do you have a history of herpes simplex (cold sores)? ________________________________

When was the last outbreak? _______________________________________________________

Do you have a history of developing keloids? _________________________________________

Have you ever been on accutane? _________________ When? ____________________________

List all surgeries that you have had (include plastic surgery): Date:

Have you or anyone in your family ever had unusual reactions to anesthesia (muscle weakness,
jaundice, breathing problems or unexpected fever(s)? YES/NO _______________________

Do you have (circle): loose or chipped teeth/caps/dentures/contact lenses/None

Have you ever seen a cardiologist? YES/NO Physician Name: __________________________

Date of last EKG: _________________________________________________________________

I acknowledge that I have disclosed my complete medical history and the above is a complete and
accurate representation of my medical and psychological status.

Patient Signature: ____________________________ Date: ________________________________
Authorization for Examination and Treatment

Name: _______________________________  Birthdate (mm/dd/yy): __________

Address: _______________________________  City: __________________________

Province: _______________  Postal Code: ___________  Home Phone: ____________

Work Phone: _______________________________  Referred by: ____________________

Health Card No. (& version code)______________________________________________

Emergency Contact Name & Number: __________________________________________

I, _______________________________ , represent to the physicians and staff that I am at least 18 (eighteen) years of age or, if not, am accompanied by a legal guardian. I hereby consent to and authorize a history examination by my doctor and such assistant or staff as may be assigned by him/her.

If appropriate, I authorize the release of any medical information for the purpose of processing insurance claims on my behalf. I authorize payments of medical benefits directly to the doctor for services provided to me. A copy of this authorization shall be considered as valid as the original. I understand that photography is a necessary part of planning and evaluating cosmetic procedures. I authorize the taking of photographs at the direction of my physician or physician delegate and under such conditions as may be approved by him/her. These photographs will be used solely for documentation purposes and will be kept confidential unless otherwise disclosed.

I understand that there is a consultation fee for the initial visit which is due at the time of my appointment unless other arrangements have been made in advance.

SIGNATURE: _______________________________  DATE: ____________

RELATIONSHIP: (circle one)  PATIENT  SPOUSE  PARENT  GUARDIAN
Payment Policy for Aesthetic Consults and/or Procedures

A VISA or MasterCard number, cash or certified cheque are required to reserve your appointment time.

Charges will not be applied to your credit card until you arrive for your treatment.

48 business hours are required for cancellation of your appointment to avoid being charged for your treatment.

If you cancel your appointment in less than 48 business hours, or fail to appear for your treatment, a charge of $100.00 will be applied to your credit card.

Although we will do our best to accommodate you, if you are late for your appointment, you may be required to rebook for another day. If this is necessary, the $100.00 fee will be waived.

** Please note that quotes and deposits are valid for 6 months **

Client signature

Date
Botox® Injections

Informed-Consent Booklet

Instructions
This is an informed-consent document that has been prepared by Dr. Mulholland to help inform you concerning Botox® injections, the risks, and alternative treatment. During your consultation, you will review the potential benefits of Botox® injections, the alternatives and all the points in this booklet. You will be able to ask any questions and be provided with answers to these questions to the best of our ability. It is important that you read this information again carefully and completely. Only when you have no questions or concerns do you initial each page, indicating that you have read and fully understood all the items it discusses. When you arrive at the end of this booklet, sign the consent for the procedure as proposed by Dr. Mulholland or your nurse injector. If you have any remaining questions, do not initial or sign the consent until they have been answered to your satisfaction.

Introduction
Botox® injections are a non-surgical procedure designed to paralyze the portions of overactive facial muscles that cause deep furrows, creases and fine wrinkles in the face. Botox® is a sterile, vacuum-dried form of purified botulinum neurotoxin type A complex, produced from a culture of the A strain of bacteria called Clostridium Botulinum. Although the Clostridium bacteria causes botulism, the Botox® extract does not. The Botox® extract is the purified, sterilized product from the bacteria and is a potent localized muscle, paralytic agent. Botox® contains a small amount of pasteurized human albumin. No cases of viral diseases have ever been identified for albumin. Botox® has been used safely for many years in the treatment of muscle disorders of the eyes and voicebox. Its most recent application has been in the treatment of cosmetic wrinkles, creases and lines in the face. Botox® is a simple injection performed in the office by Dr. Mulholland, one of the clinic dermatologists or a SpaMedica® nurse injector. The improvement in the wrinkles begins 5–7 days after the injection and lasts for 3–6 months. It may be repeated indefinitely.

Alternative Treatment
Alternative forms of treatment or management consist of not treating the wrinkles or creases and continuing to use camouflage makeup. Topical wrinkle creams or Retin-A may add some minor improvement. Microdermabrasion and Pulsed Light therapy, called WrinkleLite® and/or FotoFacial® can provide noticeable improvement in fine wrinkles without any recovery or down time (ask our staff about these treatments) and are often performed in conjunction with Botox®. Injectable treatments such as collagen, Hyaluronic Acids, and/or Microfat may help fill out the

Patient Initials ________
wrinkle. Implantable substances such as Softform (Gortex) or Alloderm may help fill out a defect. Topical laser treatment (CO₂ or Erbium) may improve or eliminate certain wrinkles. Cosmetic plastic surgery procedures such as Endoscopic Browlift, Eyelid Tucks or Face-Neck Lifts may also improve the creases or wrinkles.

**Potential Benefits of Botox®**

Prolonged softening of the fine lines, wrinkles, creases and furrows of the forehead, eyes and neck, creating a more serene-looking face with fewer active muscles and creases.

**Risks of Botox® Injections**

**Pain/Discomfort:** There is a minor degree of discomfort from the small-gauge needle that is inserted under the skin. There is a slight burning discomfort as the Botox® is injected into the muscle. Most patients find the process less painful than an immunization. The Botox® treatment only takes a few minutes to complete and is performed in the office.

**Bruising/Swelling:** Most patients have some swelling in the injection area for a couple of hours. It is rare to develop bruising after, but if this were to occur, it should disappear in 7–10 days and can be camouflaged with makeup immediately following treatment.

**Infection:** Like any injection technique, an infection may rarely occur (less than 0.5% risk) and can usually be treated with an oral antibiotic. Severe infections, although exceedingly rare, may require a drainage procedure or surgery.

**Treatment Failure:** Occasionally, the Botox® may fail to completely paralyze the facial muscle or soften the wrinkle and a repeat treatment within 2 weeks may be necessary. In the rare event that the initial Botox® injection failed to exhibit a clinical effect, there will be no charge for the subsequent single retreatment session.

**Long-term Effects:** The duration of improvement with the Botox® varies between patients, but generally, 3–6 months of decreased muscle activity and wrinkle improvement may be achieved. Repeat treatments can be performed but prolonged use over many years may result in a permanent weakness of muscle function.

**Pregnancy:** Botox® should not be used while pregnant as there is a risk of premature delivery. If there is any chance that you may be pregnant, you should first exclude the possibility with a pregnancy blood test, or not have the Botox®.

**Lactation:** There is no known risk of Botox® during lactation but, if you are concerned, we recommend postponing your Botox® until you have completed breastfeeding.
Asymmetry: When two sides of the face are being treated for the same problem, there may be some asymmetries that result between the Botox® performed on one side and the same treatment on the other side.

Functional Problems: Although extremely rare, if the Botox® treatment is too effective or there is subcutaneous migration of the substance, functional or esthetically displeasing effects may occur such as Brow Ptosis (drooping of the brow), Eyelid Ptosis (subtle drooping of an eyelid), Diplopia (double vision), Lagophthalmous (weakness of eye closure) or a smile droop. Fortunately, these side-effects are extremely rare and temporary (as the Botox® effect wears off in a few months). Depending upon the area treated, smile and lip asymmetry, failure of adequate lip closure, articulating abnormalities, swallowing and coughing may be affected.

General Body Symptoms: These occur very rarely (less than 0.1%) but can include skin rash, itchiness, general malaise, headaches, drowsiness, fever or flu-like symptoms that last for several hours or several days. These symptoms are temporary and may be remedied with a plain Tylenol or ibuprofen as directed on the bottles’ instructions.

Additional Surgery Necessary
Should any of the aforementioned or other complications occur, additional procedures or other treatments may be necessary. Even though risks and complications occur infrequently, the risks cited and those you have just reviewed are those risks particularly associated with Botox® injections. Other complications and risks can occur but are even more uncommon.

The practice of medicine and surgery is not an exact science. Although good results are expected, there is no guarantee or warranty expressed or implied on the results that may be obtained.

Health Insurance
Most health insurance companies including OHIP, exclude coverage for cosmetic surgical operations such as Botox® injections. Please carefully review your health insurance subscriber-information pamphlet. Generally, complications arising from such surgery are covered by health insurance.

Financial Responsibilities
The cost of surgery involves several charges for the services provided. The total includes fees charged by Dr. Mulholland, the cost of surgical supplies, anaesthesia, nursing costs and outpatient facility charges. Depending on whether the cost of surgery is covered by an insurance plan, you will be responsible for necessary co-payments, deductibles, and charges not covered. Additional costs may occur should complications develop from the surgery. Secondary surgery or facility day-surgery charges involved with revisionary surgery would also be your responsibility.

Patient Initials __________
Disclaimer

Informed-consent documents are used to communicate information about the proposed surgical treatment of a disease or condition, along with disclosure of risks and alternative treatment(s). The informed-consent process attempts to define principles of risk disclosure that should generally meet the needs of most patients in most circumstances.

What Dr. Mulholland has discussed with you and included again in this booklet are the material risks, both common and uncommon, that he feels a reasonable person would want to know, understand and consider in trying to decide if Botox® injections are something they would like to proceed with. However, informed consent documents should not be considered all inclusive in defining other methods of care and risks encountered. Dr. Mulholland may provide you with additional or different information which is based on all the facts in your particular case and the state of medical knowledge.

Informed-consent documents are not intended to define or serve as the standard of medical care. Standards of medical care are determined on the basis of all of the facts involved in an individual case and are subject to change as scientific knowledge and technology advance and as practice patterns evolve.

It is important that you read the above information contained on this and all preceding pages carefully and have all of your questions answered before signing the consent on the next page. Questions and concerns can be addressed by contacting the office in Hamilton at 1-800-561-3376 or in Toronto at (416) 922-2868 and speaking with Dr. Mulholland (pager (416) 402-7381).
Consent for Surgery/Procedure or Treatment

1. I hereby authorize Dr. ________________ and such assistants as may be selected to perform the following procedure or treatment:

2. I recognize that during the course of the operation and medical treatment or anesthesia, unforeseen conditions may necessitate different procedures than those above. I therefore authorize the above physician and assistants or designees to perform such other procedures that are in the exercise of his or her professional judgment necessary and desirable. The authority granted under this paragraph shall include all conditions that require treatment and are not known to my physician at the time the procedure is begun.

3. I consent to the administration of such anesthetics considered necessary or advisable. I understand that all forms of anesthesia involve risk and the possibility of complications, injury, and sometimes death.

4. As part of the requirements of Accreditation of Ambulatory Surgical Facilities, your chart may be subject to a peer review for quality control.

5. I acknowledge that no guarantee has been given by anyone as to the results that may be obtained.

6. I consent to the photographing or televising of the operation(s) or procedure(s) to be performed, including appropriate portions of my body for medical, scientific or educational purposes. These photographs may be used for medical meetings, advertising, or any promotional or public relations purposes.

7. For purposes of advancing medical education, I consent to the admittance of observers to the operating room.

8. I consent to the disposal of any tissue, medical devices or body parts, which may be removed.

9. I authorize the release of my Social Insurance Number to appropriate agencies for legal reporting and medical-device registration, if applicable.

10. I have been advised not to bring any valuable items on the day of my procedure including but not limited to: valuable clothing, watches, jewelry, glasses and dentures. SpaMedica® is not responsible for any items lost or stolen during my stay.

Patient Initials __________

SpaMedica® Franchisee Clinical Training Manual
VII – 6.5
11. I understand that the signature of the witness (if a non-physician) on this document indicates only that the signing of my name has been observed and not that the witness has necessarily provided information regarding the procedure.

12. IT HAS BEEN EXPLAINED TO ME BY MY PHYSICIAN IN A WAY THAT I UNDERSTAND:
   a. THE ABOVE TREATMENT OR PROCEDURE TO BE UNDERTAKEN
   b. THERE MAY BE ALTERNATIVE PROCEDURES OR METHODS OF TREATMENT
   c. THERE ARE RISKS TO THE PROCEDURE OR TREATMENT PROPOSED
   d. ANY QUESTIONS I MAY HAVE ASKED HAVE BEEN ANSWERED TO MY SATISFACTION

I CONSENT TO THE TREATMENT OR PROCEDURE AND THE ABOVE LISTED ITEMS (1–12). I AM SATISFIED WITH THE EXPLANATION.

Patient or Person Authorized to Sign for Patient Please Print Name Here

Date Witness

Patient Initials ________
Botox® Injections

Who is a Candidate?
• Patients with expression lines/facial wrinkles that persist despite autologen/collagen or laser treatments.

Intended Results
• The muscle is paralyzed over a period of several days and the expression line softens dramatically, becoming less noticeable.
• Results last 3–4 months, when a repeat injection can be performed.

Procedure Description
• Botox® is an injectable drug that paralyzes small areas of muscle for 3–4 months.
• It is injected around deep expression lines of the forehead and bridge of nose that are caused by overactive muscles of expression.
• The muscle is paralyzed over a period of several days and the expression line softens dramatically, becoming less noticeable.
• This procedure takes about 15 minutes to perform.

Recovery and Healing
• Most patients return to work the next day with very minor bruising that will disappear quickly and can be camouflaged with make-up.

Other Options
• Additional procedures that may enhance the result are Laser Resurfacing, Brow lift, or Blepharoplasty.

Insurance Guidelines
• Botox® injection is considered cosmetic and therefore is not covered by insurance. The patient is responsible for payment.

Surgical Fee Range
• From $300.00 to $1,200.00
# Facial Injectables

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<thead>
<tr>
<th>Date</th>
<th>Area Injected</th>
<th>Product</th>
<th>Amount</th>
<th>Lot#</th>
<th>Pregnant</th>
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</table>

Client name: ____________________________

Notes:

________________________

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________________________
Review of Facial Muscles

Specific muscles that are treated with Botox® are listed below and on the following page is a diagram of location of the muscle. A good knowledge of anatomy of facial muscles is a definite asset for Botox® injections.

1. Frontalis – elevator muscle of the forehead
2. Depressor Supercilii – forehead
3. Procerus – bridge of nose, between brow
4. Corrugator Supercilii – depressor of the forehead
5. Nasalis – bilateral sides of nose
6. Orbicularis Oculi – around bilateral eyes
7. Depressor Septi – under tip of nose
8. Orbicularis Oris – around mouth
9. Depressor Anguli Oris – mandible
10. Platysma – neck
11. Mentalis – chin
Pain Management

For Botox® Injections

1. SpaMedica® has a variety of anaesthetics to assist the client with management of pain.

2. Num-it™ cream, a topical anesthetic, contains Benzocaine, Lidocaine, and Tetracaine. There is also Benzocaine-free Num-it™. The cream is applied to the treatment area thick enough that you cannot see the skin below. This product will begin to numb in about 15–20 minutes. For optimal numbness of areas clients can purchase this product for $29.95 and apply up to an hour prior to treatment.

3. Our cryo cooler can be used in conjunction with Num-it™ or on its own. The cryo cooler blows cold air from a hose which is directed by either client or nurse to the injection site. This will drop the temperature of the skin so the injection can be virtually painless.

4. Be sure client is comfortable and pain-free at all times. This may mean treatment must be stopped to deliver more anesthetic to the treatment area.

Be aware of client’s conscious state; some clients can become lightheaded quite easily and must be placed in supine position until this passes. K-basins, BP cuffs, and washcloths are located in recovery room. Cold juice is available if needed.
Botox Cosmetic™ Post Treatment Instructions

1. Exercise your treated muscles by performing 10 contractions every 15 minutes for three hours.

2. It is important not to rub or massage the treated areas for 24 hours following treatment. SonoPeel®, SonoFacial®, Crystal Peel, MyoFacial® and FotoFacial® can be performed the same day but prior to your Botox® treatment.

3. Do not lie down or do strenuous exercise for 3 hours after treatment.

4. It is possible that you may experience a headache and flu-like symptoms for approximately 24–48 hours. Acetaminophen (Tylenol) may be taken for relief.

5. The redness and marks on the treated areas will likely disappear within a few hours after treatment. There is a slight risk of bruising that may last up to one week. This is always temporary and can easily be covered with makeup.

6. Botox Cosmetic™ can take up to two weeks for full effect. If you feel that you would desire more relaxation of the muscles treated, we will address this at your two week follow up appointment.

Your FOLLOW UP appointment is scheduled for _____________________________

7. Botox Cosmetic™ requires a special technique in order to customize the injections to your individual muscular structure. Therefore, over the next few months, it is important that your muscle activity recovers but that your skin is not creasing to the point from where you started.

8. Botox Cosmetic™ is a temporary procedure and at first, you may find that your treatment results will last approximately 3–4 months. If you maintain your treatment appointments with the frequency recommended, the duration of each treatment result may last longer than 4 months.

9. To achieve optimal results, you will need to repeat Botox® treatments when you notice recurrent muscle activity and crinkling of the skin.

YOUR NEXT TREATMENT IS SCHEDULED FOR ________________________________

If however, the muscle activity and fine crinkling recurs prior to this, then please call for an earlier appointment.

If you have any questions or concerns, please call SpaMedica® at (416) 922-3743, or after business hours, you can call Dr. Mulholland’s pager at (416) 402-7381.
Safety and Efficacy Report

Botulinum Toxin


New York, N.Y., and Sydney, Australia

Botulinum toxin, the causative agent of botulism, a descending muscle paralysis as a result of food poisoning, was identified in 1897. It is a cytoplasmic toxin produced by *Clostridium botulinum*, an obligate anaerobic bacterium. The first clinical application of botulinum toxin was described by Scott et al. when investigating nonsurgical treatments of strabismus in a primate model. Subsequently, botulinum toxin type A has found wide applications as a neuromuscular blocker in neurology, orthopedics, gastroenterology, and ophthalmology (Table I). Botox (Allergan, Irvine, Calif.) is approved by the Food and Drug Administration for the treatment of strabismus, blepharospasm, and cervical dystonia; approval for the cosmetic use of botulinum toxin, which is thus considered off-label use, is pending and, in fact, may be achieved by the time of this publication.

The original observation of the cosmetic effect of botulinum toxin was serendipitous. Carruthers and Carruthers noted a concomitant reduction in glabellar rhytides when injecting the corrugator supercilii muscle for benign essential blepharospasm. Since then, numerous studies have detailed the use of botulinum exotoxin for facial rejuvenation by reducing facial rhytids caused by hyperkinetic muscles of facial expression. Added to this are newer indications, including the treatment of headaches and hyperhidrosis and as an adjunct to reconstructive procedures (Table II). It is likely that we are only beginning to uncover the protean medical uses for botulinum toxin.

Mechanism

Of the eight serotypes of botulinum neurotoxin (A, B, C1, C2, and D-G), type A is the most potent and the most commonly used serotype in clinical practice. The underlying mechanism has been elucidated and involves the blockade of presynaptic acetylcholine release by binding to specific cell surface receptors. The toxin receptor complex is then internalized by endocytosis into nerve terminals, where it cleaves one of three essential proteins involved in facilitation of the release of neuro-transmitters. Muscle fibers become functionally de-innervated, which results in muscle fiber atrophy and flaccid paralysis. The onset of action is at 6 to 36 hours after exposure, with maximal effect up to 7 to 14 days. New neuromuscular junctions and axonal sprouts eventually replace the nonfunctional junctions and restore muscle function in 3 to 6 months.
Preparations and Pharmacology

Botulinum toxin type A exotoxin is available in two preparations, Botox (Allergan) and Dysport (Ipsen Ltd, which acquired Speywood in 1998, Maidenhead, U.K). Elan Pharmaceuticals (San Francisco, Calif.) recently released Myobloc, a botulinum toxin type B preparation.

The lethal dose of Botox is measured in units, with 1 U being the lethal dose of toxin causing death in 50 percent of a group of Swiss Webster mice. The lethal dose of toxin causing death in 50 percent of humans has been estimated to be between 2800 and 3500 U. Each vial is a lyophilized complex consisting of 100 U of toxin (10 percent variation), 0.5 mg of human albumin, and 0.9 mg of sodium chloride.10

Table I
Disorders Treated with Botulinum Toxin*

<table>
<thead>
<tr>
<th>Focal dystonias</th>
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<tbody>
<tr>
<td>Essential blepharospasm</td>
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<tr>
<td>Spasmodic torticollis and cervical dystonia</td>
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<tr>
<td>Oromandibular-facial-lingual dystonia</td>
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<tr>
<td>Laryngeal dystonia</td>
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<tr>
<td>Occupational cramps</td>
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<tr>
<td>Limb dystonia</td>
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<tr>
<td>Dystonic tremor</td>
</tr>
<tr>
<td>Nondystonic excessive muscle contraction</td>
</tr>
<tr>
<td>Back spasm</td>
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<tr>
<td>Bladder detrusor-sphincter dyssynergia</td>
</tr>
<tr>
<td>Bruxism and temporomandibular joint pain</td>
</tr>
<tr>
<td>Gastrointestinal: achalsia, anismus (constipation), cricopharyngeal spasm, lower esophageal sphincter spasm, rectal spasm, anal fissure, anal and duodenal sphincter</td>
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<tr>
<td>Hemifacial spasm</td>
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<tr>
<td>Congenital nystagmus</td>
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<tr>
<td>Spasticity: stroke, cerebral palsy, head injury, paraplegia, multiple sclerosis spasticity</td>
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<tr>
<td>Muscle contraction headaches</td>
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<tr>
<td>Pelvirectal spasms (vaginismus)</td>
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<tr>
<td>Stuttering</td>
</tr>
<tr>
<td>Other involuntary movements</td>
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<tr>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>Essential tremor</td>
</tr>
<tr>
<td>Hereditary chin tremor</td>
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<tr>
<td>Palatal myoclonus</td>
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<tr>
<td>Tics</td>
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<tr>
<td>Other applications</td>
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<tr>
<td>&quot;Protective&quot; ptosis</td>
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<tr>
<td>Aesthetic (see Table II)</td>
</tr>
<tr>
<td>Facial nerve disorders</td>
</tr>
<tr>
<td>Soft-tissue augmentation</td>
</tr>
<tr>
<td>Parotid gland fistula</td>
</tr>
<tr>
<td>Essential hyperhidrosis</td>
</tr>
<tr>
<td>Migraine and tension headache</td>
</tr>
</tbody>
</table>

Dysport uses column-based purification and requires 2.5 to 5 times more dosage than Botox to produce equivalent effects. Dysport is used in Europe and the United Kingdom but is awaiting the approval of the Food and Drug Administration for use in the United States.

The third preparation, Myobloc botulinum toxin type B (Elan Pharmaceuticals), is licensed by the Food and Drug Administration for use in patients with cervical dystonias. Myobloc’s mechanism of action is by cleavage of the vesicle-associated membrane, and cross-neutralizing antibodies between serotypes are not expected. It is available in ready-to-use injectable solution vials of 2500, 5000, and 10,000 U, with dosages in the order of 5 to 10,000 U used for the treatment of spastic conditions. It is reported to have a shelf life of up to 36 months refrigerated and 9 months at room temperature. The reported advantages of Myobloc include: usefulness in patient resistant to type A, predilution, longer shelf life, faster onset of action (possibly 24 to 48 hours), and enhanced diffusion within the muscle (potentially reducing the number of injections and complications). The lethal dose of toxin causing death in 50 percent of humans is 144,000 U. The ideal dose and number of injection sites has not been elucidated for Myobloc.

Table II
Indications for the Use of Botulinum Toxin in Plastic Surgery

Aesthetic

- Glabellar (frown muscle) complex
- Orbicularis oculi muscle
- Frontalis muscle
- Platysma muscle
- Other facial muscles: orbicularis oris, mentalis, depressor anguli oris, levator labii superioris alaeque nasi, muscular hypertrophy (temporalis, masseter)
- Combined with other procedures

Other

- Soft-tissue augmentation
- Facial nerve disorders
- Breast augmentation
- Parotid gland fistula
- Headache
- Hyperhidrosis
- Gustatory sweating (Frey’s syndrome)

Investigative

- Wound healing
Reconstitution of the Toxin

The freeze-dried toxin is reconstituted with the desired volume of sterile unpreserved saline by injection with a 1-cc tuberculin syringe and a 1½ inch 25-gauge needle or diabetic syringe. The solution is then drawn into the syringe, and the 1½ gauge needle is replaced with a 1½ inch 30-gauge needle used for injection. Two areas of controversy relating to the preparation of botulinum toxin type A are appropriate dilution of the reconstituted toxin and length of viability (and method of storage) of the reconstituted toxin. Unless otherwise stated, these data are for Botox, the most widely used preparation.

Unpreserved normal saline is the manufacturer’s suggested diluent. Lowe et al. suggested the use of preserved normal saline as an alternative to prolong activity. A recent study examined the addition of 1% lidocaine with epinephrine and concluded that the immediate paralyzing and anesthetic effect was beneficial in estimating the eventual effect of Botox. However, using local anesthetic concurrently precludes immediate muscular contraction following injection. This maneuver may enhance toxin uptake and help to evenly distribute its action.

The toxin is unstable and easily denatured. Klein emphasized that the diluent should be drawn into the vial by vacuum and not agitated, though others remove the rubber stopper entirely. In addition, alcohol applied to bottle tops or skin should be left to evaporate because it may denature the toxin on contact. The volume of dilution ranges from 1 to 8 ml per 100 U.

Storage of reconstituted solution. The length of viability of the reconstituted solution kept in a refrigerator or refrozen has also been subject to debate. The reconstituted solution should be stored at 2° to 8° Celsius. Although the manufacturer recommends that the product be used within 4 hours, there is wide variation in reported activity from solutions kept from 12 hours up to 30 days. Lowe showed that 40 to 50 percent of potency is lost after 7 days of storage and that minimal effect is seen after 14 days. In a recent poll of practitioners, 46 percent store their solution for 1 week before discarding it. Two studies that investigated freezing the solution at -20° Celsius reported conflicting data.

Clinical Efficacy

Thorough knowledge of muscular anatomy, awareness of potential complications, and appropriate injection technique are important to achieve reproducible results with botulinum toxin. These requirements are summarized in a number of review articles and educational media, which are recommended for further study. Table II summarizes the indications for the use of botulinum toxin in plastic surgery.
Common Aesthetic Indications

Since Carruthers’ original report for glabellar rhytides, the indications for Botox injections have expanded from the upper third of the face gradually downward into the neck (Table II). By paralyzing underlying mimetic muscles, dynamic frown lines can be effaced, producing reduction of furrows and wrinkles.

Glabellar complex. A number of studies have established the safety and efficacy of botulinum toxin type A in the treatment of glabellar folds relating to the corrugator, depressor supercilii, and procerus muscles (frown muscle complex).4,22-25 This remains a highly popular site for treatment.

Recent studies have focused on selective paralysis of the depressors allowing the antagonist muscles to produce a “chemical” browlift.26-29 Selectively paralyzing middle, central, and temporal depressors to varying degrees can alter the position of the eyebrow.

In the glabella, upper eyelid ptosis has been reported from paralysis of the levator aponeurosis. In Allergan’s multicenter Food and Drug Administration study, ptosis occurred in 5.4 percent of patients. Injecting the patient while upright, careful pretreatment planning, subcutaneous rather than intramuscular injection, low volume and high concentration of injectant, and repeat contractions of the levator following Botox administration can minimize these complications.30,31 Ptosis can be treated with Naphcon A Ophthalmic (naphazoline hydrochloride/pheniramine maleate) (Alcon Laboratories, Fort Worth, Texas), one to two drops in the affected eye up to four times daily, or with Iopidine Ophthalmic Solution 0.5% (apraclonidine hydrochloride) (Alcon Laboratories), one to two drops in the affected eye after ophthalmologic evaluation.

Orbicularis oculi. A number of studies have reported the use of botulinum toxin to reduce crow’s feet by paralyzing the lateral fibers of the orbicularis oculi muscle.21,30,32-37 The use of botulinum toxin as primary treatment for lower-lid orbicularis hypertrophy, fine lower periorbital wrinkles, and eyelid wrinkles, particularly in Asians,38 though not performed routinely, has also been reported. This can produce a more annular appearance of the palpebral aperture but can inadvertently produce ectropion and skin redundancy with accentuation of infraorbital rhytids.37

In the periorbital region, periocular injection can result in diplopia, ptosis, and lower lid malposition.32 Injecting in an arc pattern at least 1 cm away from the bony orbital margin can minimize these complications.

Frontalis. The treatment of forehead rhytids by direct paralysis of the frontalis has been reported in a number of studies.36,39,40 Overparalysis of the frontalis can produce inadvertent complete or partial brow paresis, resulting in an asymmetric or “cockeyed” appearance or uncomfortably low eyebrows.

Low-volume high-concentration botulinum toxin type A dilution to smooth forehead wrinkles (and limit inadvertent diffusion) rather than complete paralysis of the frontalis, avoiding paralysis
of the lower 1 cm of muscle, or concomitant paralysis of the sub-brow orbicularis oculi depressor are alternative treatment strategies to preserve muscle function. The advantages cited using these techniques are partial preservation of facial expression and avoidance of brow ptosis.

**Platysma.** Brandt and Bellman were the first to report the use of botulinum toxin injection into the platysma to correct neck bands. The rationale for the selective paralysis of the platysma is to allow the supramandibular mimetic muscles, working through the superficial musculoaponeurotic system, to elevate both muscle and skin redundancy. In more recent studies this indication has been refined to show maximal benefit for mild-to-moderate age-related changes. In addition, Matarasso et al. expanded the indications to include patients with residual banding following facialplasty surgery.

In the neck, dysphagia has been reported from paralysis of the muscles of deglutition and the larynx. The effect is usually temporary, but it can be treated with diet alteration and chemical stimulation of gastrointestinal motility.

**Other facial muscles.** Alteration of the nasolabial fold by paralysis of the levator labii superioris alaeque nasi muscle and smoothing of upper lip wrinkles by paralysis of the orbicularis oris have been reported. The results in this area are limited by the coexistence of static rhytides requiring other methods of therapy and excess mobility of the soft tissues, which can produce unacceptable flaccidity and effects on speech, mastication, and taste. An exception to this is hyperkinesis of the mentalis, which produces furrowing and cabling of the chin but which can be dramatically improved by botulinum injection. Muscular hypertrophy of the masseter and the temporalis have been successfully managed by repeated denervations with Botox.

**Combination with other rejuvenation treatment.** Botulinum toxin type A is increasingly being used in combination with surgical and nonsurgical techniques for facial rejuvenation. Fagien reported its use in combination with a variety of facial procedures, including CO₂ laser ablation for the treatment of rhytids in the lateral canthus and perioral region and as an aid to reduce tension during lateral retinacular suspension and browlift. Guerrissi reported the use of Botox intraoperatively during face-lift or blepharoplasty procedures and maintained that direct injection produces significantly longer paralysis.

**Other Indications**

**Soft-tissue augmentation.** A number of studies support the combined use of botulinum toxin type A with soft-tissue augmentation using alloplast or fat grafting. Denervation serves at least three purposes: (1) It eliminates or reduces the dynamic/muscular component of rhytide formation. (2) It has been theorized as increasing the longevity of the implant by reducing the supposed mechanical inflammatory influence on the atrophy of the implant. (3) It may reduce the immediate microextrusion at the injection sites simply by repetitive muscular action.

**Facial nerve disorders.** Clark and Berris reported the use of Botox to regain facial symmetry following facial nerve paralysis by temporarily weakening the functional side. Indications for
Botox for treating facial asymmetry and facial palsy now include the treatment of synkinesis following neuromuscular graft or transfer, facialplasty, congenital lower lip palsy, Frey’s syndrome and the intentional creation of ptosis for corneal protection.

Miscellaneous indications. Senior reported the use of Botox in conjunction with subpectoral breast augmentation to reduce pain due to pectoral muscle spasm. Botulinum toxin has also been successfully used to diminish the cholinergic parasympathetic secretomotor fibers for the treatment of parotid gland fistula.

Expanded indications. Wheeler was the first to postulate that paralysis of the pericranial musculature using botulinum toxin may improve chronic tension-type or migraine headaches. This was subsequently supported in clinical trials and was noted anecdotally in patients undergoing botulinum toxin type A injection for aesthetic indications. Furthermore, as a result of this experience, Guyuron et al. showed that surgical resection of the corrugator supercilii muscle can eliminate or significantly reduce the incidence of migraine headaches by up to 80 percent.

Another recent indication for botulinum toxin type A injection has been for the treatment of focal axillary and palmar hyperhidrosis. Injections are done superficially or subdermally in a radial pattern. Doses in the range of 50 U are sufficient. When used in the palm, the toxin should be delivered intradermally to avoid paralysis of the intrinsic hand muscles. After ensuring treatment efficacy and absence of complications following treatment of the ipsilateral palm, and possibly the fingers, the contralateral palm can be treated.

Investigative Research
Gassner et al. recently reported an interesting primate study that showed improvement in scar healing following administration of Botox. The rationale for this approach was to reduce tension across a healing wound by paralyzing the underlying mimetic muscles.

Safety and Complications
In the 20 years since the clinical use of botulinum toxin type A began, there have been only rare reports of major systemic reactions of hypersensitivity following treatment for any indication. Cobb et al. details the only clinical case of a botulism-like syndrome resulting in respiratory arrest following administration of Botox for muscle spasticity. In general, the main untoward effects of botulinum toxin administration for facial rejuvenation are a loss of facial expression (masklike facies), incomplete muscle paralysis with residual rhytids, and unwanted muscle paralysis from the spread of neuromuscular blockade to adjacent sites.

The contraindications to botulinum toxin use are summarized in Table III. These are based on theoretical interactions with drugs and intrinsic muscle disease, which could prolong its neuromuscular blockade.
Complications can be categorized as local, immunologic, or systemic. Local complications such as pain, edema, erythema, ecchymosis, headache, and short-term hyperesthesia can be related to the injection site. Matarasso summarized techniques to minimize these local complications, the most notable of which occur when the toxin diffuses to surrounding muscles. Latimer et al. also reported a case of necrotizing fasciitis following Botox injection in an immunocompromised elderly patient. Lu et al. showed no deterioration in nerve fiber histology following intraneural injection of Botox in an animal model.

Systemic reactions include nausea, fatigue, malaise, and other flulike symptoms, and distant rashes. Distant neuromuscular effects have been documented but only from single-fiber electromyographic studies. The significance of these findings is unclear. Immunologic complications include acute type I reactions and may be attributable to the human serum albumin, which has been reduced to 20 percent of the original volume for studies on patients with cervical dystonia. There have been no reports of this complication since 1997.

**Therapeutic Failure**

Therapeutic failure from botulinum toxin A can result from the presence of circulating neutralizing antibodies. Immunoresistance has been reported to occur in 3 to 5 percent of patients treated for cervical dystonia.

The development of antibodies seems to correlate with an increasing number of injections, length of treatment, and total cumulative dose of toxin. Since its use for aesthetic indications, we have encountered only one patient who was resistant to treatment, presumably because of the neutralizing effect of the antibodies. Limiting the total amount of toxin to less than 100 U per session and avoiding booster injections for a minimum of 3 months are recommended to prevent their formation. Northview Pacific Laboratories Inc. (Berkeley, Calif.) offers Botox antibody testing from serum transported at -20° Celsius. A lesser amount of protein complex per vial (ng) presumably will diminish immunogenicity. Botulinum toxin type B (Myobloc) is currently available and can be used as an alternative in patients with immunologic resistance to botulinum toxin type A.

<table>
<thead>
<tr>
<th>Table III</th>
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<tbody>
<tr>
<td><strong>Contraindications for Treatment with Botulinum Type A Exotoxin</strong></td>
</tr>
<tr>
<td>Hypersensitivity to ingredients (albumin)</td>
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<tr>
<td>Neuromuscular disease: myasthenia gravis, Eaton Lambert syndrome</td>
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<tr>
<td>Patients treated with aminoglycosides, penicillamine, quinine, calcium channel blockers</td>
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<tr>
<td>Pregnancy/lactation</td>
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<tr>
<td>Patients on anticoagulation therapy/ aspirin</td>
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<tr>
<td>Phobia of injection</td>
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<tr>
<td>Poor psychological adjustment</td>
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</table>

Finally, patients unprepared for the paralyzing effect and changes in facial structure can experience untoward psychological adjustment after therapy. Careful patient selection and counseling are important in both prevention and treatment.

**Conclusions**

Demand by patients for a rapid, safe rejuvenation treatment with minimal recuperative time has resulted in an exponential increase in the interest in and use of botulinum toxin A. According to the American Society for Aesthetic Plastic Surgery, Botox injection was the number one procedure overall for 2000, increasing 120 percent compared with 1999, and 1583 percent compared with 1997.\(^8\) Numerous clinical studies document its safety and efficacy. Toxicity is mild, with most adverse events related to paralysis of unwanted musculature.

The indications for botulinum toxin therapy have expanded, and newer investigations will undoubtedly uncover additional indications for temporary neuromuscular blockade in a variety of clinical situations.

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**References**


Botulinum Toxin Type A Is a Safe and Effective Treatment for Axillary Hyperhidrosis Over 16 Months

A Prospective Study

M. Naumann, MD; N. J. Lowe, MD, FRCP; C. R. Kumar, PhD; H. Hamm, MD; for the Hyperhidrosis Clinical Investigators Group

Objective: To evaluate the safety and efficacy of botulinum toxin type A (BTX-A) (BOTOX) over 16 months in the treatment of bilateral primary axillary hyperhidrosis.

Design: A 16-month study with initial double-blind randomization to 50 U of BTX-A or placebo per axilla. After 4 months, participants could receive up to 3 further treatments with open-label BTX-A over 12 months.

Setting: Fourteen dermatology or neurology clinics in Germany, Belgium, and the United Kingdom.

Participants: Of 207 individuals aged between 17 and 74 years who had persistent bilateral primary axillary hyperhidrosis that interfered with daily activities, 174 (84%) completed the study. The baseline gravimetric assessment was a spontaneous sweat production of 50 mg or greater in each axilla prior to initial treatment.

Main Outcome Measures: At week 4 after each treatment, the response rate of subjects who had at least a 50% reduction from baseline in axillary sweating, as measured by gravimetric assessment, was evaluated. Adverse events were spontaneously reported throughout the study, together with quality-of-life parameters and assessment of neutralizing antibodies to BTX-A.

Results: Over the 16-month period, 356 BTX-A treatments were given to 207 subjects. After placebo treatment, the response rate at week 4 was 34.7%. After the first, second, and third treatment with BTX-A, response rates at week 4 were 96.1%, 91.1%, and 83.5%, respectively. For subjects receiving more than 1 treatment, the mean duration between BTX-A treatments was approximately 7 months; however, 28% of subjects completed the study after only 1 BTX-A treatment. Subjects' satisfaction after treatments was consistently high, their quality of life improved, and there was a reduction in the impact of the disease on their lives. The safety profile of BTX-A after repeated treatments was excellent and no confirmed positive results for neutralizing antibodies to BTX-A occurred.

Conclusion: Repeated intradermal injections of BTX-A over 16 months for treatment of primary axillary hyperhidrosis is safe and efficacious.

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Primary focal hyperhidrosis is a chronic idiopathic disorder of excessive sweating that most often affects the axillae, palms, soles, and forehead. This condition can cause significant problems in private and professional life, and has been shown to have an adverse impact on the daily activities of those affected by this disorder.2 The eccrine sweat gland is innervated by the sympathetic nervous system, but its principal periglandular neurotransmitter is acetylcholine. Botulinum toxin type A (BTX-A) inhibits the release of acetylcholine from the presynaptic membrane of cholinergic neurons and thus is a possible form of treatment for hyperhidrosis.2 In a recent large, multicenter, randomized, controlled, double-blind study comparing the effects of a single treatment of BTX-A (BOTOX; Allergan Inc, Irvine, Calif) with those of placebo in primary axillary hyperhidrosis, 93.8% of subjects had a 50% reduction from baseline in axillary sweating at week 4 and were classified as responders.3 The safety profile of BTX-A injections was similar to that of placebo. These results confirmed previous reports of the successful use of BTX-A for this condition.4,11

Hyperhidrosis is a chronic condition, and as such requires a safe and lasting treatment. At present, the only lasting treatments are surgical, and consist either of sympathectomy or the removal or reduction of the sweat glands by excision, curettage, or liposuction. However, these methods carry the general risks associated with surgery and can also lead to compensatory sweating.12 Although BTX-A has been shown to be effective in treating hyperhidrosis with 1 treatment, few data are available on the efficacy...
and safety of repeated treatments. In addition, there has been no formal assessment of antibody formation after treatment, which is a theoretical risk due to the protein content of BTX-A. Furthermore, systematic quality of life (QOL) information after repeated treatments was not previously known. All these points are covered in this study, whose objective was to evaluate the safety and efficacy of BTX-A over 16 months for the treatment of bilateral primary axillary hyperhidrosis.

METHODS

STUDY SETTING

This study was carried out at 14 dermatology or neurology clinics in Germany, Belgium, and the United Kingdom in compliance with the ethical principles of the Declaration of Helsinki (October 1996); with the informed consent regulations of each participating country; and with the International Conference on Harmonization of Good Clinical Practice guidelines. All subjects who wished to participate in the study gave written informed consent prior to any study-related procedures.

PARTICIPANTS

Subjects could be included in the study if they were aged between 18 and 75 years and had idiopathic persistent bilateral primary axillary hyperhidrosis that interfered with their daily activities. Spontaneous sweat production in each axilla of at least 50 mg, measured over 5 minutes at room temperature and at rest, was required prior to initial treatment. Women of childbearing potential had to have a negative urinary pregnancy test prior to each study treatment. Only subjects who continued beyond their initial double-blind treatment were included in this study report.

STUDY DRUG TREATMENT

Initially, subjects were randomly assigned to receive either 50 U of BTX-A per axilla (a total dose of 100 U) or placebo in a double-blind manner. The dilution used was 4 mL of unpreserved 0.9% sterile sodium chloride solution per 100-U vial. The hyperhidrosis area was identified using the Minor iodine-starch test, and BTX-A or placebo was administered by means of 10 to 15 intradermal injections distributed evenly within the hyperhidrotic area. Subjects were followed up for 16 weeks (the method used during this phase is provided in detail with the publication of the study results). After the 16-week follow-up visit, subjects could receive up to 3 additional open-label treatments with BTX-A. They were treated when they requested it, provided that sweat production in each axilla was at least 50% of the baseline value recorded at their entry into the study. Moreover, at least 16 weeks had to elapse between treatments and no treatments were permitted after week 48. Subjects were assessed at weeks 4 and 16 following each treatment. All subjects completing the study had an exit visit at week 66.

EFFICACY PARAMETERS

The primary efficacy parameter was the percentage of treatment responders. This was defined as subjects who showed a reduction in axillary sweating of at least 50% of their baseline value recorded immediately prior to the most recent treatment, measured by gravimetric assessment of spontaneous axillary sweat production over 5 minutes at room temperature and at rest. The primary endpoint was week 4 after treatment. Other efficacy assessments included the percentage change from baseline in sweat production; the mean raw gravimetric values at each assessment; the mean duration of effect (time between treatments); the change in the size of the sweat-producing area (measured by the Minor iodine-starch test); the subjects' global assessment of treatment satisfaction (based on a 0-3 point scale, from +4 for complete abolishment of signs and symptoms to –4 for very marked worsening of signs and symptoms); and serum antibody testing for BTX-A-neutralizing antibodies using a standard mouse protection assay.

SAFETY PARAMETERS

Safety was assessed by the incidence and severity of spontaneously reported adverse events (AEs) and measurement of vital signs (blood pressure, heart rate, and body temperature).

QOL ASSESSMENTS

Quality-of-life assessments of the impact of hyperhidrosis on various aspects of the patient's life (eg, daily activities, work/productivity, and satisfaction with treatment) were carried out using the Short Form-12 (SF-12) questionnaire and the Hyperhidrosis Impact Questionnaire, an instrument developed by the University of Wurzburg and Allergan, Inc. This report addresses satisfaction with BTX-A treatment compared with previous treatments; satisfaction with ability to perform work activities; limitations while in public places; limitations while meeting people for the first time; and number of times per day a change of clothes is needed.

STATISTICAL ANALYSIS

A target number of subjects of 200 was considered sufficient to provide data on long-term safety (over 16 months). All efficacy and QOL data were summarized by treatment cycle using descriptive statistics and frequency tables. All analyses were intent to treat, i.e., outcomes were analyzed for all subjects who were randomized to treatment. For the gravimetric assessment, missing values were replaced using the last-observation-carried-forward method. Measurements taken immediately prior to each treatment were considered the baseline data for that cycle and bilateral values were averaged for each subject at each time point. For the primary parameter of treatment responder rates, the 95% confidence interval was calculated. Within-group changes from baseline were tested at the .05 level against the null hypothesis that there was no change from baseline. The duration of effect was assessed by calculating the mean time between 2 consecutive treatments.

For the QOL questions relating to the impact of hyperhidrosis on limitations in meeting people for the first time and being in public places, a scoring system from 0 (no limitations) to 4 (extremely limited) was used. For assessment of patient satisfaction the proportion of subjects responding that they were "very or somewhat satisfied" or "much more or somewhat more satisfied" was calculated for each parameter. Means (SDs) were calculated using the total number of subjects who answered a particular question as the denominator.

The safety analyses included all subjects who received at least 1 treatment with BTX-A or placebo. All AEs were tabulated and summarized by relationship to study treatment and severity (mild, moderate, and severe). For the analysis of AEs by treatment cycle, events were counted in the treatment cycle in which they first began. For blood pressure, heart rate, and body temperature, mean baseline values and mean changes from baseline (measurement prior to each treatment) were calculated for each treatment cycle.

RESULTS

STUDY POPULATION

A total of 207 subjects were enrolled in 14 dermatology or neurology centers in Europe; 6 in Germany, 6 in the United
Kingdom, and 2 in Belgium. A total of 336 BTX-A treatments were given during the 16-month study period. Of the 207 study subjects, 38.6% (80) had 1 treatment, 44.9% (93) had 2 treatments, 14.9% (50) had 3 treatments, and 3.4% (4) received only placebo during the study period. None had the maximum of 4 treatments allowed. Eighty-four percent of the subjects (174/207) completed the 16-month study. Only 33 subjects discontinued, 1 because of an AE not related to treatment, 1 because of pregnancy, 1 because of protocol violation, 1 because of a lack of efficacy, and 17 because of other reasons (eg, failure to return for a scheduled visit, not meeting the treatment criteria although additional treatment was wanted, and personal reasons); 12 were lost to follow-up.

The overall mean age of the population was 31 years. There were similar numbers of men and women enrolled (46.4% [96/207] and 53.6% [111/207], respectively), and the population was primarily white (98.1% [203/207]).

EFFICACY RESULTS

The response rates following each treatment with BTX-A were consistently high and were substantially better than the response rates following treatment with placebo (Figure 1). Although only descriptive statistics were performed, there appears to be no major diminution of effect with repeated treatment cycles. Response rates were 96.1%, 91.1%, and 83.3% at week 4 after the first, second, and third treatments, respectively, compared with 34.7% after treatment with placebo. A similar pattern was seen for the mean percent change from baseline in sweat production and the mean raw values at each visit, with BTX-A causing a greater reduction in these values than placebo (Table 1). The size of the hyperhidrotic area, as measured by the Minor iodine-starch test, also markedly decreased following each treatment with BTX-A (Table 1).

A prolonged duration of effect was seen following each BTX-A treatment, with an overall mean duration of 30.6 weeks between any 2 consecutive treatments (range, 15.4-51.3 weeks). However, this calculation only applies to subjects who received at least 2 BTX-A treatments, and 28% of subjects who completed the 16-month study period did not receive additional treatments. In a substantial proportion of subjects the effect duration may thus be considerably longer.

Subjects rated their satisfaction with BTX-A treatment very high. Mean scores at week 4 were +3.5, +3.4, and +3.3 after the first, second, and third treatments, respectively. This indicates marked improvements in the subjects' assessment of their signs and symptoms. In comparison with placebo, assessments of treatment satisfaction showed little change from baseline (a mean rating of +1.4 at week 4).

Of the 207 subjects treated over the 16-month study period, only 1 possible seroconversion from negative to positive for neutralizing antibodies to BTX-A occurred. This subject had a negative antibody test result at enrollment and a positive result at the end of the 16 months after 1 treatment. However, this subject was still classified as a responder on completion of the study and did not receive additional treatments. However, subsequent test results during follow-up after completion of the study were negative for BTX-A antibodies after completion of the study. Furthermore, this subject was retreated with BTX-A after the end of the study and still showed a marked response to treatment, with a reported complete disappearance of axillary sweating 7 days after injection.

SAFETY RESULTS

The safety profile of BTX-A was excellent, with no increase in the number of AEs with additional treatment cycles. Of the 49.3% of subjects (102/207) who reported at least 1 AE, 13.5% (28/207) reported events that were considered treatment related (Table 2). The most common AE was injection (predominantly common cold), followed by flu syndrome, and a perceived increase in nonaxillary sweating (which occurred at several sites including the forehead, hands, face, feet, back, chest, trunk, and groin). The latter was the most common treatment-related AE, with an incidence of 4.3% (9/207), although no clear pattern to this sweating was seen. A total of 11 subjects reported serious AEs during the study, and there was 1 death due to myocardial ischemia complicated by pulmonary bronchitis. None of the serious AEs were considered to be related to the study drug. One subject became pregnant during the study approximately 4 months after receiving BTX-A treatment, and the pregnancy continued to term without complications with the delivery of a healthy boy. No changes of clinical relevance were seen in any of the vital signs recorded.

QUALITY OF LIFE

The results of the QOL assessments are shown in Table 3 and Figure 2. Following each BTX-A treatment the robust positive effects on QOL parameters were maintained, with a sustained reduction in the adverse impact of hyperhidrosis and a high level of satisfaction.

COMMENT

Many studies have shown that BTX-A is a highly effective treatment option for axillary hyperhidrosis, but sufficient long-term treatment data are lacking for this chronic condition. This is the first large-scale study systematically collecting data on the effects of longer-term, repeated treatment of hyperhidrosis with BTX-A. Of the
207 subjects who were recruited, 174 completed the 16-month study and thus provided substantial longer-term safety and efficacy data. The results of this study demonstrated that repeated treatment with BTX-A over 16 months is safe; that BTX-A maintains its efficacy over repeated treatment cycles; and that it has a positive impact on patients' QOL. However, these results are applicable only to the formulation used (BOTOX), and not necessarily to other formulations or serotypes.

Since hyperhidrosis is a chronic condition, and the known pharmacologic properties of BTX-A indicate that the treatment effect will not be permanent, it is likely that subjects will request repeated treatments. With 96.1%, 91.1%, and 83.3% of our subjects experiencing a 50% or greater reduction in sweating after the first, second, and third treatments, we demonstrated that BTX-A reduces the amount of sweating over repeated treatments. This robust response reflects the results of previously published studies, where similar levels of response were following a single administration of BTX-A.3,11,13 It also confirms the data of a recent report, where intradermal injections of BTX-A repeated over 3 years in a limited number of subjects with axillary and palmar hyperhidrosis were as effective as the first treatments.18 However, in our study, not all subjects required additional treatment and even fewer needed more than 2 treatments; hence, the data for the second and third treatments include those whose duration of response was...
somewhat shorter. Although they had a good response, they may be considered a less responsive cohort. It is anticipated that treatment optimization may enhance their response in the clinical setting. There was no indication that response increased with repeated treatment.

The decrease in sweat production after each treatment indicates that disuse atrophy of the sweat glands is not occurring. This is in agreement with previous quantitative histological studies, which have shown that even after sympathectomy or in severe autonomic neuropathy with anhidrosis, there is no evidence of sweat gland atrophy. Thus, denervation of sweat glands, either chemically (by botulinum toxin) or by degeneration of sudomotor fibers, has no obvious influence on sweat gland morphology.

Additional treatment in this study was permitted every 16 weeks based on subject request, and although a return to 50% of the baseline value was required, complete return to the baseline value was not mandatory. This is thought to give a reasonable reflection of clinical practice, where patient request is likely to be the primary factor in the decision to retreat. However, although subsequent treatment was allowed after 16 weeks, the average time between treatments was 7 months, and in 20% of subjects who completed the study, no additional treatment was needed following their first BTX-A treatment. This indicates a much longer duration of effect in a substantial number of subjects. Although a longer duration of effect has been suggested in a recent publication after treatment with a much higher dose of BTX-A (200 U of BTX-A per axilla, for a total dose of 400 U), these data were generated from particularly low subject numbers, with no quantitative inclusion criteria, no objective measures of treatment success, and no objective criteria for receiving additional treatments. Comparison of these data with those of our present study is therefore not appropriate, and we consider that they do not provide a foundation for recommending treatment at this dose.

The formation of neutralizing antibodies with repeated BTX-A treatments was not apparent in this study. Only 1 seroconversion from negative to positive was recorded; however, this subject remained a responder to treatment, and follow-up after completion of the study showed a negative result for BTX-A-neutralizing antibodies. Furthermore, the subject responded to subsequent treatment. This result is consistent with the low protein load of this specific BTX-A formulation, which is believed to result in a low risk of neutralizing-antibody formation.

### Table 3. Quality-of-Life Outcomes After Repeated Treatments

<table>
<thead>
<tr>
<th></th>
<th>Placebo Treatment</th>
<th>1st BTX-A Treatment</th>
<th>2nd BTX-A Treatment</th>
<th>3rd BTX-A Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limitation score on being in public places</strong>††</td>
<td>n</td>
<td>Mean (SD) or %</td>
<td>n</td>
<td>Mean (SD) or %</td>
</tr>
<tr>
<td>Baseline</td>
<td>48</td>
<td>2.4 (1.2)</td>
<td>195</td>
<td>2.1 (1.3)</td>
</tr>
<tr>
<td>Week 4</td>
<td>48</td>
<td>1.9 (1.2)</td>
<td>197</td>
<td>0.2 (0.6)</td>
</tr>
<tr>
<td>Week 16</td>
<td>44</td>
<td>1.8 (1.4)</td>
<td>172</td>
<td>0.4 (0.6)</td>
</tr>
<tr>
<td><strong>Limitation score on meeting people for the first time</strong>††</td>
<td>n</td>
<td>Mean (SD) or %</td>
<td>n</td>
<td>Mean (SD) or %</td>
</tr>
<tr>
<td>Baseline</td>
<td>48</td>
<td>2.7 (1.2)</td>
<td>195</td>
<td>2.5 (1.3)</td>
</tr>
<tr>
<td>Week 4</td>
<td>48</td>
<td>2.9 (1.3)</td>
<td>196</td>
<td>0.3 (0.7)</td>
</tr>
<tr>
<td>Week 16</td>
<td>44</td>
<td>1.8 (1.4)</td>
<td>172</td>
<td>0.6 (0.8)</td>
</tr>
<tr>
<td><strong>Subjects changing clothes more than twice a day</strong>‡</td>
<td>n</td>
<td>Mean (SD) or %</td>
<td>n</td>
<td>Mean (SD) or %</td>
</tr>
<tr>
<td>Baseline</td>
<td>48</td>
<td>76</td>
<td>190</td>
<td>76</td>
</tr>
<tr>
<td>Week 4</td>
<td>47</td>
<td>68</td>
<td>190</td>
<td>76</td>
</tr>
<tr>
<td>Week 16</td>
<td>42</td>
<td>64</td>
<td>175</td>
<td>14</td>
</tr>
<tr>
<td><strong>Proportion of subjects going out or meeting people</strong></td>
<td>n</td>
<td>Mean (SD) or %</td>
<td>n</td>
<td>Mean (SD) or %</td>
</tr>
<tr>
<td>Baseline</td>
<td>40</td>
<td>18</td>
<td>168</td>
<td>18</td>
</tr>
<tr>
<td>Week 4</td>
<td>9</td>
<td>44</td>
<td>70</td>
<td>94</td>
</tr>
<tr>
<td>Week 16</td>
<td>40</td>
<td>18</td>
<td>170</td>
<td>92</td>
</tr>
</tbody>
</table>

Abbreviation: BTX-A, botulinum toxin type A.

*Scoring system: 0 = not limited; 1 = somewhat limited; 2 = moderately limited; 3 = quite a bit limited; 4 = extremely limited.

(Data are given as mean (SD)).

*Data are given as percentage.

### Figure 2. Quality of life: satisfaction with current treatment compared with prior treatments (percentage of patients much more or somewhat more satisfied). BTX-A indicates botulinum toxin type A.
In conclusion, these results represent the first robust longer-term study on the effects of repeated treatment with BTX-A in a substantial number of subjects. Treatment with 50 U of BTX-A is useful and safe over 16 months for subjects with idiopathic axillary hyperhidrosis, and it contributes significantly to improving their quality of life.

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REFERENCES


Botox for the Treatment of Dynamic and Hyperkinetic Facial Lines and Furrows: Adjunctive Use in Facial Aesthetic Surgery

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Our improved understanding of the pathophysiology of facial lines, wrinkles, and furrows has broadened the treatment options for a variety of facial cosmetic dilemmas. The persistence or recurrence of certain facial rhytids after surgery has confirmed the lack of full comprehension of their origin. Glabellar forehead furrows (frown lines) and lateral canthal rhytids (crow's feet) have been the most popular facial lines that have been shown to be mostly the result of regional hyperkinetic muscles, and their eradication may be more suitable, at times, to chemodenervation than to soft-tissue fillers, skin resurfacing, or surgical resection. Aesthetic surgical procedures that have yielded suboptimal results may also occur from failure to recognize other causative factors including hyperkinetic or dynamic musculature, which may contribute to the etiology of the visible soft-tissue changes and lack of persistent effect after surgery. Chemodenervation with botulinum toxin A (Botox) has proven to be useful both as a primary treatment for certain facial rhytids and as an adjunctive agent for a variety of facial aesthetic procedures to obtain optimal results. (Plast. Reconstr. Surg. 112 (Suppl.): 408, 2003.)

The logical approach to facial rejuvenation is facilitated when one first (through an assessment and diagnosis of the nature of the pathology) differentiates quantitative from qualitative changes in facial soft tissue. Quantitative and malpositional changes have traditionally required a surgical approach: the excision or repositioning of soft tissue (skin, muscle, and fat). Conversely, qualitative changes may require the fortification of the soft tissue by mechanical, chemo- or laserexfoliation, or augmentation of a particular soft-tissue plane. Most recently, a focus has been directed to prevention with sun protection, skin care, and improved nutrition as well as the realization of other causative risk factors that include hyper-functional and dynamic components of facial lines.

Hyperdynamic (hyperkinetic, hyperfunctional) or long-term facial muscular animation seems to contribute to the etiology of many undesired facial rhytids and furrows. The presumption that facial lines were the result of, in part, forces generated by local muscular actions was first observed postmortem on a microanatomic basis by Pierard and Lapiere.¹ Facial denervation of particular facial muscles has been shown to improve overall facial appearance not only by temporarily eliminating rhytids but also by improving malpositional changes of the overlying soft tissue and possibly the results of particular facial aesthetic surgical procedures discussed herein.

HISTORY

The interest in chemodenervation and specifically the use of botulinum toxin as a therapeutic agent for weakening particular skeletal muscles dates back to the 1920s. Almost 30 years later, pediatric ophthalmologist Dr. Alan Scott collaborated with Dr. Edward J. Schantz² in the preparation of a batch of crystalline toxin to determine its effectiveness as an injectable agent for producing transient weakness of extraocular muscles and permanent changes in ocular alignment.³ This had remained the source of botulinum toxin type A until 1997 as the commercially available product, Botox (Allergan, Inc., Irvine, Calif.). After many years and experiences with this product, supplies

were finally exhausted, and Botox was reformulated to what is currently used worldwide.

The toxins of *Clostridium botulinum* are classified into eight immunologically distinguishable exotoxins. The type A toxin is most easily produced in culture and was the first one obtained in a highly purified, stable, and crystalline form. The principal effect of muscle paralysis is caused by the inhibition of the release of acetylcholine at the neuromuscular junction. The paralytic effect of the toxin is dose related, with the peak of the effect occurring 5 to 7 days after injection. Denervated muscle histopathology shows muscle atrophy and a mild degree of demyelinating changes at the nerve terminal. Axonal nerve sprouting seems to be a usual response to chemodenervation and may diminish true clinical muscular atrophy (hence long-term beneficial effects in some regions). Single-fiber electromyography studies indicate abnormal neuromuscular transmission in muscles distant from the site of injection despite the absence of clinical weakness, indicating the potential for spread of the toxin that could be significant at higher doses. These observations and effects supported by some good experimental data provide a rationale for treatment protocol for the use of Botox in a variety of disorders.

Botox is presently approved for the treatment of strabismus and blepharospasm associated with dystonia (including benign essential blepharospasm or VII cranial nerve disorders) in patients 12 years of age and above. Although not (FDA) approved for its use, many have experience with a multitude of other clinical applications of botulinum toxin, including the treatment of bruxism, stuttering, painful rigidity, lumbosacral pain and back spasms, radiculopathy with secondary muscle spasm, spastic bladder, achalasia, tremor, involuntary tics, tension headaches, neuromuscular paralysis, lower eyelid spastic entropion, aberrant regeneration of the facial nerve (after Bell’s palsy etc.), acquired nystagmus, corneal pathology/amblyopia therapy aided by the effects of occlusion, and in periocular reconstructive surgery.

Many experienced clinicians had noted the improvement of facial rhytids in their patients who had received Botox for a variety of facial spastic disorders (Fig. 1). This discovery, in conjunction with a prelude to a better understanding of the anatomic basis of several facial frown lines, forced the question of the possible benefit of chemodenervation for certain facial wrinkles.

The treatment of glabellar frown lines (Fig. 2) enjoyed early attention owing to the experience of those who treated patients with benign essential blepharospasm, which typically involved injection of toxin into the medial eyebrows (corrugators). Other targeted facial hyperkinetic lines that gained early popularity included the treatment of lateral canthal rhytids (crow’s feet) and horizontal forehead furrows. More recently, the applications have extended to congenital and traumatic facial asymmetry, postsurgical eyebrow asymmetry (including dyskinesis) and facial paralysis, orbicularis hypertrophy (of the lower eyelids), perioral rhytids, hyperfunctional midfacial animation lines, soft-tissue malposition, and as an adjunct to endoscopic forehead lifts, laser skin resurfacing and injectable agents for soft-tissue augmentation.

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**Fig. 1.** *Left* An image comparing this treated side of a patient with long-standing aberrant regeneration of the facial nerve from Bell’s palsy to the untreated left side. *Right* After several years of treatment with Botox for unilateral blepharospasm, there is a notable asymmetry of visible (reduced) rhytids on this right (left panel) side. *Right* Unreated side. This left periorbital demonstrates a significant qualitative change (more rhytids) compared with the treated side (left panel).
FIG. 2. (Above) Before treatment with Botox, this patient exhibits significant vertical (glabellar frown lines) furrows, especially with animation. (Below) One week after treatment with Botox to the glabella region. Patient is attempting to frown.

**Facial Wrinkle Anatomy and Physiology**

Understanding the anatomic relationships and functional features of a variety of facial muscles to the surrounding soft tissue provides the additional necessary groundwork for the treatment rationale of chemodenervation for a variety of aesthetic displeasures.  

The palpebral component of the orbicularis oculi surrounds the pretarsal and proximal septal aspects and is essentially the “sphincter” muscle of the eyelids responsible for blinking and gentle eyelid closure. Its direct antagonist is the levator palpebrae muscle. Forceful contraction of the orbital component of the orbicularis oculi induces concentric folds emanating from the lateral canthus. Some of the fibers of the superomedial orbital component function as depressors of the medial eyebrow. These fibers constitute the depressor supercili. The superolateral orbital orbicularis oculi acts, in part, as a depressor of the lateral eyebrow. The corrugator supercilii serves to draw the eyebrow inferiorly and medially, and as such produces the vertical glabellar frown lines. The procerus muscle, in part, draws the medial (head of the) eyebrows inferiorly and produces the transverse wrinkles over the bridge of the nose. The main antagonist of all of the eyebrow depressors is the frontalis muscle. The zygomaticus major muscle draws the angle of the mouth superiorly, laterally, and posteriorly with actions of laughing, smiling, and chewing. The zygomaticus minor muscle functions as one of the lip elevators and with the zygomaticus major contributes to the nasolabial fold. Forceful contraction of the zygomaticus muscles in animation (smiling) produces synergistic effects in the periorbital region, accentuated by the contraction of the orbital orbicularis and enhancing the radially oriented folds at the lateral canthus, exaggeration of the skin tension lines of the midface, and recruitment of lower eyelid soft-tissue redundancy (by elevating the cheek) that is not evident in the nonanimated state. The orbicularis oris is responsible for forceful lip closure and serves as a sphincter to the mouth. Contraction of this muscle induces folds that radiate from the vermilion border. This muscle in part is an antagonist to the lip elevators. An understanding of the basic anatomy of facial expression is essential not only for the appropriate approach to the treatment of hyperkinetic facial lines and furrows but also a methodology to avoid complications discussed later.
PREPARATION AND DILUTION

Botulinum toxin A is a labile but highly potent toxin. Each vial (supplied by Allergan) contains approximately 100 units of toxin in a crystalline complex. The toxin should be stored immediately upon receipt in the office freezer at $-5^\circ$C or lower in this crystalline form. Toxin reconstitution should be performed just before actual injection for maximal potency. Dilution should be followed carefully with the diluent of nonpreserved saline as instructed for specific concentrations as described in the package insert; however, most clinical uses of Botox are well suited for a dilution of 2.5 units per 0.1 ml, which is easily obtained by mixing 4.0 ml of nonpreserved saline to the vial. The use of preserved saline has been suggested by some authors for hope of extending the shelf life and potency once reconstituted; however, there has been concern regarding the effect of the preservative, turbulence with dilution, and agitation in denaturing (hence reduced effect) of the delicate toxin.

Once reconstituted, the toxin should be used as quickly as feasible. The package insert suggests that the product be used within 4 hours; however, many users have noted reasonable effects with the use of the product for up to 30 days. In my experience, a notable decline in clinical potency occurs after 48 hours of reconstitution that may affect depth of focal paralysis and longevity of effect. Further, the relative stability of the reconstituted toxin is felt to be best maintained by refrigeration (not freezing), and it is suggested that the product be kept cool at every opportunity. To the best of my knowledge, however, there have been no studies to substantiate or refute claims of the duration of potency of the toxin after reconstitution.

Early investigators had suggested up to 10 to 20 units or more per site to affect the targeted muscles of facial expression. However, one can achieve effects with far less toxin (2.5 units per site) and maintain longevity of effect for comparable periods of time. In my experience, this dose is effective for an average of 4 to 6 months. These lower doses in smaller volumes also serve to reduce unwanted effects and complications (see below). Concentrations much less that 2.5 units per 0.1 ml can induce a weakening effect on the targeted muscle but seem to do so for a much shorter duration.

Additionally, men (or even women with clinically evident large hypertrophic target muscles—particularly corrugators or frontalis muscles) seem to require a slightly higher dose per injection site (up to 5.0 units per site), otherwise resulting in only mild to moderate improvement of hyperfunctional rhytids with shorter duration of effects. Diluted toxin should be drawn up into 1.0 ml (T.B. syringes) through an 18-gauge needle to minimize physical trauma to the toxin.

TECHNIQUE OF INJECTION: GLABELLA, LATERAL CANTHUS, AND FOREHEAD

As in all procedures, patients desire maximum benefit with minimal side effects and morbidity. It may therefore be advisable that patients temporarily discontinue aspirin and other drugs that can affect bleeding time before Botox injection, similar to how you might instruct your patients before surgery. This, however, is not mandatory but may reduce or eliminate facial bruising that can last for several weeks. If minimal to no bruising occurs after injection of Botox, patients can typically return to work unnoticed less than 1 hour after treatment.

After the toxin is drawn up by 18-gauge needles into 1.0 ml syringes, the needle is then replaced by a short, 30-gauge needle for injection. The use of local anesthesia is relatively contraindicated and unnecessary. Alcohol may be applied to the injection sites but should be allowed to dry fully before injection of toxin owing to toxin lability. I currently do not employ the use of electromyographic guidance, as I find this cumbersome and unnecessary. Electromyographic guidance may, however, be useful when getting started with chemodenervation for general orientation. Some of the literature on the cosmetic applications of botulinum toxin A describes and illustrates sites for injection with reference points targeted at the actual wrinkle line rather than the causative muscle. Skin demarcations and sites of eventual injections of toxin can be made over the presumed belly or muscle mass of the regional muscle of facial expression and not typically at the site of the maximal dermal depression, which at times may be quite distant from the mass of the effecting muscle. For the larger, deeper muscles such as the corrugator supercilii, it is most useful and efficacious to inject toxin deep to the overlying muscles (frontalis or orbicularis) or directly into the
mand. I have found it helpful to isolate the area by placing the thumb of the nondominant hand beneath the eyebrow and superior orbital rim (Fig. 5). This serves to steady the patient’s head and target region, orient the injector to the supraorbital notch and neurovascular bundle, and avoid inadvertent injection into the orbit. The needle is inserted to the presumed level of the muscle mass of the corrugators followed by injection of the toxin. The thinner, orbicularis muscle (and even the procerus muscle) responds favorably to a more superficial, subcutaneous injection of Botox (Fig. 6).

Unlike the other larger muscles of facial expression that may require direct contact of the toxin to the majority of the muscle mass, hence

Fig. 4. Approximate areas of injection of Botox for a variety of facial rhytids and furrows. Dark blue dots show approximate sites for injection of the corrugator supercilii muscles. The light blue dot shows the area of injection of the procerus muscle. By selective weakening or paralyzing the medial brow depressors (corrugator and procerus muscles), eradication of vertical (glabellar frown line) forehead furrows is often accompanied by medial brow elevation. Red dots show the approximate areas for lateral canthal/orbital orbicularis injection to reduce or eliminate crow’s feet. Injection immediately beneath the lateral eyebrow (orange dot) can induce relative brow elevation. The green dots at the malar area show the approximate site of the proximal aspect (origin) of the zygomaticus major muscle. Chemodenervation in this area can affect (reduce) the nasolabial fold and reduce hyperdynamic smile lines and recruitment of lower eyelid and canthal rhytids.

Fig. 5. This patient is receiving treatment with Botox for vertical/glabellar frown lines. The injector straddles the thumb and forefinger of the opposite hand around the orbital rim for orientation of the periorbital to steady the patient’s head. This aids to prevent an intraorbital injection or bleeding from injection at the supraorbital notch. The fluid of injection should be visible during injection as a deep soft-tissue elevation.

Fig. 6. This patient is receiving treatment with Botox to lateral canthal rhytids and the lateral sub-brow region to enhance lateral brow elevation. Notice that the injections in this region are given in the subcutaneous plane rather than the intramuscular.
requiring injection more directly into the muscle, the relatively thin orbicularis muscle (and isolated procerus) seems to be satisfactorily affected by injecting the toxin into the subcutaneous space overlying the muscle. This not only reduces the chance of significant ecchymoses but may therefore maintain the potency that could be reduced by bleeding. Additionally, injection into the subcutaneous space may allow for more local (even) diffusion over the targeted muscle and provide an additional safety barrier to structures deep to the muscle. For lateral canthal rhytids (crow’s feet), three or four injections are given with particular avoidance of the pretarsal orbicularis of the upper and lower eyelid (Fig. 7). This is achieved by directing needle insertion temporal to the lateral canthus near the lateral orbital rim (Fig. 4) and distant to the eyelid margin (Fig. 6). The procerus muscle can be injected at one or two sites just beneath the (skin) transverse wrinkle at the nasal bridge. This superficial plane also avoids orbital injection. Hyperkinetic horizontal forehead furrows\textsuperscript{11,12,14,16} seem to respond favorably to either subcutaneous or intramuscular injection of the toxin, presumably since the frontalis is the only active muscle in this region. Weakening, rather than complete frontalis denervation, may also be preferable in some individuals to avoid brow ptosis. These injections are most effective by administering a uniform grid,\textsuperscript{16} whereby approximately nine or more sites are injected across the forehead (Fig. 8). Three or more sites over each side are positioned in a vertical line above the mid-eyebrow. Additional sites are positioned vertically in the mid-forehead region. This affords focal frontalis muscle weakening at the medial aspects of each muscle group. A more homogeneous treatment of the forehead avoids focal areas of residual function that can become quite noticeable in lieu of complete absence of adjacent furrows. Typically, 2.5 units (0.1 ml) are administered at each site. Injections over the lateral eyebrow are minimized or avoided to reduce the potential for lateral eyebrow ptosis. Contrary to much of the reported concern regarding staying upright or avoiding physical activity
for several hours after the injections. I have not found it necessary to instruct patients on this. Cosmetics may be applied immediately after injection.

Although, theoretically, the effect of the toxin is described as occurring between 3 and 7 days after injection, I have noted consistently an earlier onset of effect compared with those patients who experience Botox for the treatment of eyelid and facial spastic disorders such as benign essential blepharospasm and hemifacial spasm. Occasionally, a patient-recipient of Botox for hyperkinetic facial lines experiences the effects within several hours for reasons not well understood. Although the immediate treatment benefits reflect the toxins’ ability to temporarily weaken or paralyze those muscles responsible for the muscular component of the hyperkinetic facial lines, the theoretic suggestion (not yet proven) is that repeated injections into the same muscles over time could produce a sort of disuse atrophy that would limit the development of certain facial lines in younger individuals and possibly eliminate or reduce (over time) established facial lines and furrows.

However, because of the entity of axonal sprouting (discussed earlier) and the fact that patients typically return for additional treatment after the muscles have regained near complete clinical function (i.e., the wrinkle has returned), true long-term muscular atrophy may not be the only possible cause for long-term improvement in some individuals that may also reflect (in part) alteration in facial animation patterns and remodeling of the overlying soft tissue.

**Extended Uses of Botox in Facial Aesthetic Surgery**

**Facial Nerve Disorders**

Botulinum toxin A also has been shown to be useful for a variety of other facial cosmetic problems. I have found it useful in even subtle cases of aberrant regeneration of the facial (seventh cranial) nerve (for instance after recovery of a Bell’s palsy), which although it may not induce a significant visual impairment, poses significant embarrassment to some (Fig. 9). At times, very low doses are quite effective such as 1.0 unit or less per site administered over the pretarsal orbicularis in the same manner given for the treatment of (benign essential) blepharospasm. Botox can also be used to achieve symmetry in congenital and

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area injections (2.5 units/0.1 ml) into the lateral sub-brow region (Fig. 4).

Ocularis (oculi) muscle hypertrophy of the lower eyelids may also be effectively treated using very low concentrations (1.0 unit/0.05 ml) of toxin into or overlying the visibly hypertrophic (thickened) muscle. Low doses may still cause a mild but often acceptable degree of lower eyelid retraction. Two or three injections are administered at the central lower eyelid and lateral canthus overlying the affected areas. Higher concentrations, however, may induce significant paralytic eyelid retraction or ectropion and may also impair the nasolacrimal pumping action of the orbicularis muscle, inducing epiphora.

Similar caution and consideration can be applied to tone down the effects of the zygomaticus major and minor muscles. The zygomaticus major muscle not only affects the elevation of the corner of the mouth with smiling but in doing this recruits the enhancement of crow’s feet, which can be quite exaggerated in some individuals. The zygomaticus minor muscle originates similarly to the zygomaticus major muscle and inserts more medially into the upper lip. Both of these muscles, in part, when active, deepen the nasolabial fold. By using low dosages (2.5 units/0.2 ml) in the proximal aspects (far from the mouth) near the areas of origin, with efforts made to inject toxin mostly at the level of the edge of the inferior aspect of the orbicularis of the lower eyelid (Fig. 4), one can soften their additive effect on the lateral canthal rhytids and nasolabial folds (Fig. 12). One or two injections administered over the mid to lateral malar eminence are usually satisfactory in obtaining the desired effect without incurring complications, particularly paralysis of the ipsilateral upper lip.

Finally, Botox has been shown to be useful as a primary treatment in reducing fine perioral rhytids (lip stick lines). \(^{11,12,19}\) Approximately 1.0 to 1.5 units of toxin is injected adjacent to the fine vertical rhytids overlying the orbicularis oris muscle close to the vermilion ridge. An added noted aesthetic effect at times with this treatment is the appearance of fuller (pseudo-augmented) lips because the sphincter muscle is weakened along the vermilion border to assume a more everted position (Fig. 13).

**Enhanced Surgical Results with Chemodenervation**

Those experienced with CO\(_2\) laser abrasion have noted the first recurrent rhytids in the

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**Fig. 12.** (Left) This patient had undergone a mid-face/cheek lift several years previously but desired improvement of the appearance of the cheek and canthal lines with smiling. (Right) After treatment with Botox to the lateral canthus and proximal aspect of the zygomaticus major muscle. This latter effect reduces the effect of wide smiling on the recruitment of lower eyelid/cheek and canthal rhytids and diminishes the depth of the nasolabial fold.
lower eyelid and lateral canthus. At times, in patients where there is significant hyperdynamics especially at the lateral canthus and perioral region, the rhytids can actually appear worse after laser skin resurfacing by any method (Fig. 14). Pretreatment with Botox may improve the smoothing effect of the new remodeled/resurfaced skin long enough to effect more permanent eradication of wrinkles\textsuperscript{11,12} (Fig. 15).

Similarly, this approach may be beneficial in pretreatment for those individuals who will undergo brow lifting procedures by enhancing results from weakening the inferior vector force (lateral orbital orbicularis oculi muscle, the antagonist to the frontalis muscle and eyebrow elevation), which would promote and provide maintenance of the elevated eyebrow position (Fig. 16).

Reinforcement during lateral canthal suspension procedures such as the lateral tarsal strip\textsuperscript{20} or the lateral retinacular suspension\textsuperscript{21} can be aided by injecting Botox (2.5 units/0.1 ml) around the lateral canthus as in the method described for the treatment of lateral
canthal rhytids that not only diminished the regional rhytids but also reduced local orbicularis oculi function that, in part, may compromise the position and security of the lateral canthus with repeated muscular contraction (Fig. 16).

Another very useful application of Botox has been in patients with soft-tissue contour abnormalities or atrophy that benefit from the coincident use of both modalities. Preceding the injection or surgical placement of the soft-tissue augmentation material by approximately 1 week, Botox is administered for focal weakness or paralysis. Injection of the dermal filler, subdermal fat, or surgical implantation (of alloplastic or allogeneic material) is then given into the paralyzed or muscularily weakened area (Fig. 17). The denervation serves at least three purposes. First, it eliminates or reduces the dynamic/muscular component of rhytid formation. Second, there is some theoretic suggestion that it may increase the longevity of the dermal implant by reducing the supposed mechanical inflammatory influence on atrophy of the implant. Third, it may also simply reduce the immediate microextrusion at the injection sites by repetitive muscular action, etc. This can be seen by weakening the medial brow depressors before administering collagen or fat to the glabella or injecting Botox to the lip elevators and depressors before soft-tissue augmentation of the nasolabial folds and in lip augmentation, respectively. Dosages to the glabella are similar to those used in the primary treatment to any particular region. Lower dosages (1.25 units/0.1 ml) may be applied to the lips before augmentation. The combination of chemodenervation and soft-tissue augmentation (particularly autologous collagen) in these areas has been shown to be highly synergistic.\textsuperscript{11,12,22}

\textbf{OTHER OBSERVATIONS}

Not uncommonly, patients after receiving Botox (not necessarily particular to one facial region but more prevalent in those injected in or around the eyebrows and forehead) note a generalized (almost euphoric) feeling of im-
the toxin. Most effects for the various cosmetic applications of Botox last (as in the functional/spastic disorders) between 4 and 6 months. Patients must be counseled and aware of the typical (transient) effects of chemodenervation on their hyperfunctional lines and the likely need for maintenance treatment.

**Complications**

Reported adverse reactions with the general use of Botox for all approved applications include blepharoptosis, diplopia, globe perforations, retrobulbar hemorrhage, Adies pupil, worsening of dry eye symptoms, lagophthalmos, photophobia, epiphora, ectropion, and exposure keratitis. Complications that have arisen with the cosmetic applications of Botox have included most of the above-noted reactions and additional unwanted temporary effects including ecchymoses, eyebrow ptosis and asymmetry, and mouth drop. Unwanted side effects, such as blepharoptosis and mild lower eyelid retraction (Fig. 10), typically last only a few weeks at most as the dose of migrated toxin to the affected muscle is usually significantly reduced. The temporary use of the counter ocular decongestants (eyedrops) that contain adrenergic agents (with coincidental side effects of the eyedrops that include temporary contraction of Muller’s muscle and an elevated upper eyelid margin position) for allergy/congestion (Naphcon A, Vasocon A, Opcon A) may prove beneficial to those patients who are significantly symptomatic from the transient blepharoptosis.

**Conclusions**

The use of Botox for the treatment of hyperkinetic facial lines and furrows is merely another effective primary or adjunctive therapy to offer your cosmetic patients in the spectrum of treatment options for full facial rejuvenation. Unwanted side effects can be minimized and beneficial effects maximized with a thorough understanding of the facial soft-tissue anatomy, proper patient selection, and administration of the lowest effective dosages with minimal volume of delivery. It most often does not replace surgery, skin resurfacing, soft-tissue augmentation, or skin care. However, it has been shown to be quite useful when used alone or in conjunction with the variety of treatment options to give your selected patients the most
effective and comprehensive solutions for a more youthful appearance.

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REFERENCES
Acknowledgment of Complete Comprehension

I __________________________, franchise trainee, on this date of __________ have carefully read and have a thorough understanding of every page of this chapter. I have initialed each page that signifies I have no further questions whatsoever regarding the information in this chapter, and that all my questions have been answered by the SpaMedica® franchisor trainer to my complete and total satisfaction.

Franchisee Signature  ____________________________________________________________

Name ___________________________ Date ________________

Franchisor Trainer Signature  _____________________________________________________

Name ___________________________ Date ________________