ORIGINAL ARTICLES
SPECIAL TOPIC
Journal of Drugs in Dermatology

Consideration of Muscle Mass in Glabellar Line Treatment With Botulinum Toxin Type A

Gary Monheit MD,[a] Xiaoming Lin MS RN,[b] Diane Nelson BSN MPH,[b] and Michael Kane MD[c]
[a]Total Skin & Beauty Dermatology Center, Birmingham, AL; [b]Medicis Pharmaceutical Corporation, Scottsdale, AZ;
[c]Kane Plastic Surgery, New York, NY

ABSTRACT

The introduction of botulinum neurotoxin type A (BoNTA) for the treatment of glabellar lines marked a revolution in aesthetic medicine, allowing for noninvasive facial rejuvenation and sculpting. Treatment of the glabellar area requires a thorough understanding of facial anatomy and the interaction of adjacent muscle groups with respect to facial expression. Because the muscles underlying the glabella are among the larger muscles commonly treated with BoNTA, they may require higher doses than other facial sites. In addition, men typically have a greater glabellar muscle mass than women and require larger BoNTA doses. For optimal outcomes, it is necessary to account for individual variation in muscle mass, anatomy, and function to determine the proper dose, number, and location of injections. The validated Medicis Glabellar Muscle Mass Scale was developed to facilitate research on dose adjustment for muscle mass in the glabella and can be applied as a clinical tool. This review will discuss techniques for optimizing BoNTA treatment of the glabella, with emphasis on the need to assess muscle mass in individual patients and adjust BoNTA dosing and technique accordingly.

J Drugs Dermatol. 2012;11(9):1041-1045.

INTRODUCTION

The discovery of the aesthetic applications of botulinum neurotoxin type A (BoNTA) was a revolutionary change in aesthetic medical practice, providing a less invasive approach to facial rejuvenation and sculpting to achieve a more youthful appearance.[1] Three BoNTA products are available for aesthetic use in the US: abobotulinumtoxinA (Dysport®, Medicis Aesthetics Inc., Scottsdale, AZ),[2] incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, LLC, Greensboro, NC),[3] and onabotulinumtoxinA (Botox® Cosmetic, Allergan, Inc., Irvine, CA)[4] (Table 1). Doses of different BoNTA products are not interchangeable, or even directly comparable, due to differences in production and assay methods[3,5,6]; however, the techniques for treatment are otherwise generally similar. Although these products are widely used in aesthetic treatment of different facial areas, most research has focused on the temporary improvement of glabellar lines, for which multiple clinical studies have shown that BoNTA injections are effective and well tolerated.[7-16]

Achieving the desired outcome with BoNTA while minimizing the risk for adverse events requires proper dosing and accurate placement of injections to avoid migration of the product outside the target muscle. An optimal treatment plan takes into account facial anatomy, the interactions of adjacent muscle groups, and muscle mass. The muscles underlying the glabella are, in most patients, among the larger targets for BoNTA treatment of the face and require higher doses than most other facial muscles commonly treated with BoNTA.[17] Furthermore, each of the muscles of the glabellar complex varies in mass and strength among individuals. Anatomic diagrams and bony landmarks such as the bony orbital ridge form an inadequate basis for placement of the injections; dynamic evaluation of the glabellar muscles via visualization and palpation at rest and at maximal contraction is needed to assess their location, bulk, contour, and symmetry.[17] Clinical trials have typically evaluated standardized doses of BoNTA and a fixed number of injection sites for the treatment of glabellar lines. Formal grading scales for muscle mass may improve comparability of trial data and also find clinical applications.

This review will focus on the nuances of technique, including the need to judge muscle mass in individual patients and adjust dose based on muscle mass, when using BoNTA to treat glabellar lines.

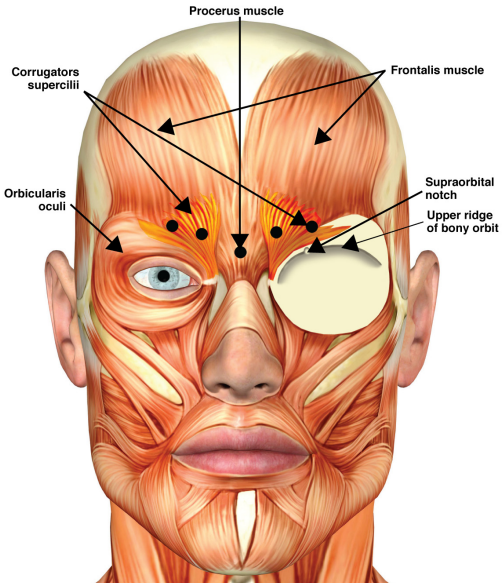
Considerations for Optimal Treatment of Glabellar Lines

Muscular Anatomy of the Glabellar Complex

Muscles of the glabellar complex responsible for the formation of frown lines include the corrugator supercilii, depressor supercilii, procerus, and orbicularis oculi para frontalis muscles (Figure 1). The corrugator supercilii lies below the frontalis muscle and functions to draw the brow medially and downward, whereas the smaller depressor supercilii is located lower than the corrugator muscle and functions to draw the medial brow downward. The procerus is located between the eyebrows and also works to depress the glabellar medial brow region. The depressor function of the glabellar complex is opposed by the frontalis muscle. This muscle is merged with the superior portions of the glabellar complex, from which it extends upwards underneath the forehead. The frontalis is the sole brow elevator.[17] Understanding of the anatomic location and interplay between elevator and depressor muscles is needed to guide injection technique in order to achieve a smooth, balanced, and aesthetically pleasing outcome with BoNTA.

The facial musculature of the individual patient (Figures 2 and 3) critically affects treatment decisions for several reasons. Gender-based differences may influence treatment decisions, and, in

FIGURE 1. Facial anatomy and injection sites for the glabellar complex; the total dose is dependent upon glabellar muscle mass, patient sex, and the desired outcome. Muscles of the glabellar complex (procerus and corrugator supercilii [orange]) are labeled, as are the adjacent frontalis and orbicularis oculi muscles. The most lateral injection points (black dots) lie on an imaginary line directly above the pupil of each eye. The bony orbital ridge and supraorbital notch (or foramen) are noted as landmarks. Injection near the supraorbital notch should be avoided; injection >1 cm superior to the bony orbital ridge is usually advisable but may be inappropriate for an individual with very low-lying corrugator supercilii muscles.



general, men have greater muscle mass than women and may have a greater threshold for response. Therefore, dosing requirements may need to be adjusted by gender to achieve optimal treatment outcomes.[12] Additionally, individual variations in muscle mass, position, frequency of use, and contractile strength necessitate the adjustment of dose and injection site location for the optimal treatment of glabellar lines.[17,18]

Validated objective scales of glabellar muscle mass in men and women have potential value for optimizing dosing early in the course of BoNTA treatment, minimizing the necessity of touch-ups, and reducing the risk of adverse effects. Several scales have been used in clinical trials to measure wrinkle severity in the glabellar area, such as the Facial Wrinkle Scale (FWS),[19] which measures wrinkle severity at maximum frown and repose on a 4-point scale from 0 (none) to 3 (severe; validation studies are lacking for this scale), and the Glabellar Line Severity Scale (GLSS),[20] which measures wrinkle severity at maximum frown on a validated scale from 0 (no lines) to 3 (severe lines).[12] However, these scales do not measure muscle mass per se.

Muscle Mass Scale Validation Study

The validated Medicis Glabellar Muscle Mass Scale (MGMMS) was developed to provide a clinically useful measure of glabellar muscle

FIGURE 2. Sample photographs of women with glabellar muscles relaxed (left) and at maximum frown (right), respectively, with small muscle mass **(A, B)**, medium muscle mass **(C, D)**, and large muscle mass **(E, F)**.

mass when considering BoNTA treatment for facial rejuvenation.[12] Medicis Glabellar Muscle Mass Scale scoring uses a 3-point scale (small, medium, and large muscle mass) and takes into consideration 4 specific features of assessment (Figures 2 and 3, and Video):

1) Wrinkle depth and depression (How deep are the wrinkles and brow depression at full contraction?)

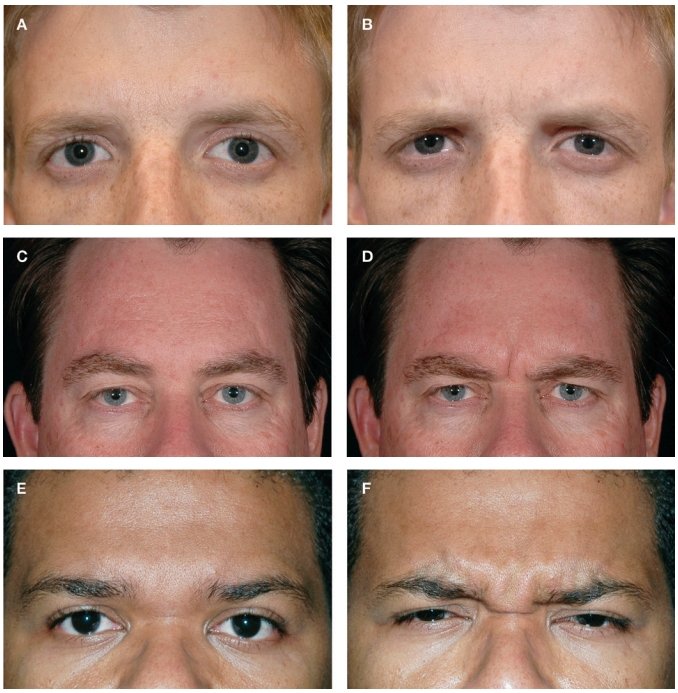
2) Inter-brow space (How much does it change from relaxation to full contraction?)

3) Glabellar muscle size and shape (Are the glabellar muscles bulging at the point of maximum frown?)

4) Shape and position of the brow (are the glabellar muscles depressed or distorted at the point of maximum frown?)

A validation study was performed to evaluate the within- and between-evaluator performance of the MGMMS. Six experienced evaluators independently examined photographs of 30 women and 30 men. The photographs displayed a frontal view of each subject's forehead and were assigned unique identifying numbers in no particular order. Evaluators made 2 rounds of assessments, separated by at least 2 weeks, using the same set of photographs on each occasion but in a different, computer-randomized order during each session. The within- and between-observer reliability of the MGMMS was demonstrat-

FIGURE 3. Sample photographs of men with glabellar muscles relaxed (left) and at maximum frown (right), respectively, with small muscle mass **(A, B)**, medium muscle mass **(C, D)**, and large muscle mass **(E, F)**.



ed using weighted kappa coefficients (separately for men and women; Table 2). Although a somewhat lower overall weighted kappa coefficient was found in the evaluation of men (within-observer, 0.719; between-observer, 0.557-0.607) compared with women (within-observer, 0.872; between-observer, 0.625-0.718), the results are consistent with substantial within-observer agreement (ie, kappa 0.60-0.79). Despite its robust validation and direct applicability to glabellar muscle mass, the MGMMS has several potential limitations. First, assessment is based on static 2-dimensional images, rather than on live assessments of patients. Additionally, a standard relationship between MGMMS results and a proper starting BoNTA dose has not yet been established.

Dosing of BoNTA to Treat Glabellar Lines

The prescribing information for each BoNTA product specifies a standard, fixed total dose for the glabellar complex (50 U of abobotulinumtoxinA, 20 U of onabotulinumtoxinA, or 20 U of incobotulinumtoxinA), but states that the location, size, and use of muscles vary significantly among individuals.[2-4] Some studies have shown that variable dosing of BoNTA can facilitate more effective treatment of glabellar lines when comparing women versus men or patients with smaller versus larger glabellar muscle mass.[12,21] Moreover, BoNTA was shown to be safe when dosage was adjusted for small, medium, or large muscle mass (ie, 50, 60, or 70 U in women, and 60, 70, or 80 U in men, respectively) in a large clinical trial.[12] Statements by consensus groups and experienced clinicians further support individualization of BoNTA dosing for achieving optimal improvement of glabellar lines (Table 1).[17,18]

"Some studies have shown that variable dosing of BoNTA can facilitate more effective treatment of glabellar lines when comparing women versus men or patients with smaller versus larger glabellar muscle mass."

A starting dose should be chosen based on a standard dose from the prescribing information or recommendations of consensus groups and experienced clinicians[17,22] and then adjusted based on individual assessment of muscle mass. Individual dose adjustment is based on clinician judgment, aided by a thorough understanding of facial anatomy (as noted previously), assessment of glabellar muscle mass, appearance at presentation (eg, presence of facial asymmetry or ptosis), and previous experience with the individual patient if he or she has received BoNTA treatment before. For new patients, it is advisable to estimate the initial dose conservatively and follow up in 2 to 4 weeks for a touch-up dose if needed. This approach requires careful clinical judgment because definitive data are lacking on how to adjust the dose and about potential risks associated with administering doses higher than those approved in the prescribing information.

Localization and Technique for Injections of BoNTA to Treat Glabellar Lines

Variation in muscle bulk, length, angle, and symmetry are particularly common for the corrugator supercilii.[23,24] Injections of BoNTA should be kept >1 cm superior to the bony supraorbital ridge (Figure 1)[2-4] if visualization and palpation clearly indicate that the belly of the corrugator supercilii lies at least 1 cm superior to the orbital ridge. In individuals whose corrugator supercilii is less than 1 cm superior to the orbital ridge, care must be taken to avoid missing the corrugator and injecting the lower margin of the frontalis, which will likely result in brow ptosis. Overdosing of the glabella can lead to excessive widening of the inter-brow space, distortion of brow contour, and loss of normal facial expression. Thus, ensuring proper placement and adjusting the dose in individuals according to muscle mass reduces the risk for adverse events associated with overdosing of smaller muscles.[2-4]

When injecting, the following points are helpful to keep in mind: grasp the target muscle (corrugator supercilii) and simultaneously press the frontalis upward to avoid injecting it.[17] Aim the needle away from the eye in order to reduce the chance of injecting behind the septum into the orbicularis oculi, thus causing upper lid ptosis (ie, eyelid droop). Although some authorities advise injecting perpendicular to the muscles,[22] angling the needle parallel to the body of the corrugator can improve the likelihood of injecting directly into the belly of the muscle. To help prevent bruising, avoid visible blood vessels while injecting and immediately apply pressure if bleeding

TABLE 1.

Botulinum Toxin Products Licensed in the US and Dosing Recommendations for Treating Glabellar Lines

Product	Manufacturer	Packaging	Inactive Components	Target Muscles	Approved Dose	Dose Range in Women	Dose Range in Men
AbobotulinumtoxinA (Dysport®)	Ipsen Biopharm Ltd.	300 U in a single-use vial	Human serum albumin and lactose	Procerus Corrugator supercilii	50 U[2]	30 U to 70 U over 5 injection sites[17]	50 U to 80 U over 5 injection sites[17]
IncobotulinumtoxinA (Xeomin®)	Merz Pharmaceuticals	50 U or 100 U in a single-use vial	Human serum albumin and sucrose	Procerus Corrugator supercilii	20 U[4]	20 U over 5 injection sites[4] (for men and women)	
OnabotulinumtoxinA (Botox Cosmetic®)	Allergan Pharmaceuticals Ireland	50 U or 100 U in a single-use vial	Human serum albumin and sodium chloride	Procerus Corrugator supercilii	20 U[3]	20 U to 30 U over 5 to 7 injection sites[18]	30 U to 40 U over 5 to 7 injection sites, sometimes more[18]

TABLE 2.

Reliability of the Medicis Glabellar Muscle Mass Scale Among 6 Raters

Weighted Kappa	Photographs of Women	Photographs of Men
Within-observer agreement (round 1 vs round 2)	0.872	0.719
Between-observer agreement (round 1)	0.718	0.607
Between-observer agreement (round 2)	0.625	0.557

Weighted kappa coefficients for within-observer reliability were graded as follows: 0-0.19 = poor agreement; 0.20-0.39 = fair agreement; 0.40-0.59 = moderate agreement; 0.60-0.79 = substantial agreement; 0.80-1.0 = almost perfect agreement.

is observed. Penetrate deeply enough through the dermis and fat layer to reach the target muscle; there should be a slight increase in resistance to needle penetration at this point. Do not go so deep as to hit the periosteum,[18] which may be painful to the patient and may result in headache. If this deep level is reached, withdraw the needle slightly and inject into the muscle.

Degree of Effect

It is possible to dose the glabellar complex to the point that there is an inability for the patient to effect any voluntary movement and an absence of normal facial expressiveness results. It is best to select a dose that will reduce wrinkles yet retain a degree of facial expression. Individual patients may request varying degrees of paresis; for example, an actor may wish to retain a greater degree of facial expression at the expense of some visible wrinkling.

Skin of Color

Genetic differences in the pharmacokinetics of BoNTA and the effects of genetic variation in acetylcholine receptors on BoNTA pharmacodynamics have not been investigated. However, it has been postulated that patients with skin of color could respond differently to BoNTA treatment than white patients owing to genetic variations that manifest as histologic differences in the dermal tissue.[17] A pooled analysis comparing patients with skin of color (n=363) with white patients (n=1653) who participated in 3 abobotulinumtoxinA clinical studies found that safety, tolerability, effectiveness, and patient satisfaction were similar regardless of race.[25] A study of onabotulinumtoxinA in 31 black women found that the maximum response rate occurred at 30 days postinjection and diminished through day 120; there was no white patient comparator population in this study.[26]

CONCLUSION

Achieving a desired aesthetic outcome with BoNTA therapy requires a thorough understanding of facial anatomy, individual patient assessment for correct injection placement, and objective assessment of muscle mass for optimal dosing. Men generally have a greater glabellar muscle mass than women and may have a greater threshold for response. Therefore, dosing requirements may need to be greater in men than in women for the optimal treatment of glabellar lines. In addition, large patient-to-patient muscle variation in mass, position, frequency of use, and contractile strength requires that dosing and injection sites be adjusted based on clinician judgment and an understanding of proper injection technique to achieve optimal aesthetic outcomes while minimizing the risk for potential adverse events.

Achieving the desired aesthetic outcome when using BoNTA for the treatment of glabellar lines is more fully optimized when therapy is based on individualized patient assessment incorporating a thorough understanding of facial anatomy, an objective assessment of muscle mass, and proper injection technique.

ACKNOWLEDGMENTS

Editorial support for this manuscript has been provided by Craig D. Albright PhD and Robert Gatley MD of Complete Healthcare Communications, Chadds Ford, PA, with funding from Medicis Aesthetics Inc., Scottsdale, AZ.

DISCLOSURES

Gary Monheit MD has served as a consultant for: Allergan, Inc., Genzyme Corporation, Johnson & Johnson Pharmaceutical Research & Development, LLC., Ipsen, Medicis Pharmaceutical Corporation, Electro-Optical Sciences, Inc., Revance Therapeutics, Galderma Laboratories, LP, Mentor Corporation, and Merz Aesthetic Pharmaceuticals GmBH, and served as a clinical investigator for: Allergan, Inc., Dermik Laboratories, Genzyme Corporation, Contura International A/S, Ipsen, Medicis Pharmaceutical Corporation, Electro-Optical Sciences, Inc., Revance Therapeutics, Kythera Biopharmaceuticals, Galderma Laboratories, LP, Mentor Corporation, and Merz Pharmaceuticals. Xiaoming Lin is Vice President of Clinical Research and Development at Medicis Pharmaceutical Corporation, Scottsdale, AZ. Diane Nelson is Director of Medical Affairs at Medicis Pharmaceutical Corporation, Scottsdale, AZ. Michael Kane MD has served as a consultant for Merz Aesthetic Pharmaceuticals GmBH, Ulthera, Inc., Kythera Biopharmaceuticals, Inc., Lithera, Inc., Allergan, Inc., Bioform Medical, Inc., Canfield Scientific, Inc., Johnson & Johnson, Medicis Pharmaceutical Corporation, Q-Med, Revance Therapeutics, Inc., Shire, Sanofi-Aventis, and Stiefel Laboratories, Inc.; served as clinical investigator for: Medicis Pharmaceutical Corporation, Q-Med, and Sanofi-Aventis; and is a significant shareholder in: Allergan, Inc., and Medicis Pharmaceutical Corporation.

REFERENCES

1. Carruthers A, Carruthers J. Cosmetic uses of botulinum A exotoxin. *Adv Dermatol.* 1997;12:325-347; discussion 348.
2. Dysport® (abobotulinumtoxinA). Full Prescribing Information, Medicis Aesthetics Inc., Scottsdale, AZ, 2010.
3. Xeomin® (incobotulinumtoxinA). Full Prescribing Information, Merz Pharmaceuticals, LLC, Greensboro, NC, 2011.
4. BOTOX® Cosmetic (onabotulinumtoxinA). Full Prescribing Information, Allergan, Inc., Irvine, CA, 2010.
5. Frevert J. Content of botulinum neurotoxin in Botox®/Vistabel®, Dysport®/Azzalure®, and Xeomin®/Bocouture®. *Drugs R D.* 2010;10:67-73.
6. Pickett A, Perrow K. Formulation composition of botulinum toxins in clinical use. *J Drugs Dermatol.* 2010;9:1085-1091.
7. Brandt F, Swanson N, Baumann L, et al. Randomized, placebo-controlled study of a new botulinum toxin type A for treatment of glabellar lines: efficacy and safety. *Dermatol Surg.* 2009;35:1893-1901.
8. Carruthers JA, Lowe NJ, Menter MA, et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J Am Acad Dermatol.* 2002;46:840-849.
9. Carruthers JD, Lowe NJ, Menter MA, et al. Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. *Plast Reconstr Surg.* 2003;112:1089-1098.
10. Cohen JL, Schlessinger J, Cox SE, et al. An analysis of the long-term safety data of repeat administrations of botulinum neurotoxin type A-ABO for the treatment of glabellar lines. *Aesthet Surg J.* 2009;29:S43-S49.
11. Fagien S, Cox SE, Finn JC, et al. Patient-reported outcomes with botulinum toxin type A treatment of glabellar rhytids: a double-blind, randomized, placebo-controlled study. *Dermatol Surg.* 2007;33:S2-9.
12. Kane MA, Brandt F, Rohrich RJ, et al. Evaluation of variable-dose treatment with a new U.S. botulinum toxin type A (Dysport) for correction of moderate to severe glabellar lines: results from a phase III, randomized, double-blind, placebo-controlled study. *Plast Reconstr Surg.* 2009;124:1619-1629.
13. Monheit GD, Cohen JL. Long-term safety of repeated administrations of a new formulation of botulinum toxin type A in the treatment of glabellar lines: interim analysis from an open-label extension study. *J Am Acad Dermatol.* 2009;61:421-425.
14. Moy R, Maas C, Monheit G, et al. Long-term safety and efficacy of a new botulinum toxin type A in treating glabellar lines. *Arch Facial Plast Surg.* 2009;11:77-83.
15. Rubin MG, Dover J, Glogau RG, et al. The efficacy and safety of a new U.S. botulinum toxin type A in the retreatment of glabellar lines following open-label treatment. *J Drugs Dermatol.* 2009;8:439-444.
16. Sattler G, Callander MJ, Grablowitz D, et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. *Dermatol Surg.* 2010;36:2146-2154.
17. Kane M, Donofrio L, Ascher B, et al. Expanding the use of neurotoxins in facial aesthetics: a consensus panel's assessment and recommendations. *J Drugs Dermatol.* 2010;9:s7-22; quiz s23-25.
18. Carruthers J, Fagien S, Matarasso SL. Consensus recommendations on the use of botulinum toxin type A in facial aesthetics. *Plast Reconstr Surg.* 2004;114:1S-22S.
19. Carruthers A, Carruthers J, Said S. Dose-ranging study of botulinum toxin type A in the treatment of glabellar rhytids in females. *Dermatol Surg.* 2005;31:414-422; discussion 422.
20. Baumann L, Brandt FS, Kane MA, et al. An analysis of efficacy data from four phase III studies of botulinum neurotoxin type A-ABO for the treatment of glabellar lines. *Aesthet Surg J.* 2009;29:S57-65.
21. Carruthers A, Carruthers J. Botulinum toxin type A. *J Am Acad Dermatol.* 2005;53:284-290.
22. Ascher B, Talarico S, Cassuto D, et al. International consensus recommendations on the aesthetic usage of botulinum toxin type A (Speywood Unit)–Part I: Upper facial wrinkles. *J Eur Acad Dermatol Venereol.* 2010;24:1278-1284.
23. Benedetto AV, Lahti JG. Measurement of the anatomic position of the corrugator supercilii. *Dermatol Surg.* 2005;31:923-927.
24. Janis JE, Ghavami A, Lemmon JA, et al. Anatomy of the corrugator supercilii muscle: part I. Corrugator topography. *Plast Reconstr Surg.* 2007;120:1647-1653.
25. Taylor S, Callender V, Lin X. Onset and durability of response of abobotulinumtoxinA for reduction of glabellar lines in patients with skin of color. Presented at: American Academy of Dermatology, February 4-8, 2011; New Orleans, LA.
26. Grimes PE, Shabazz D. A four-month randomized, double-blind evaluation of the efficacy of botulinum toxin type A for the treatment of glabellar lines in women with skin types V and VI. *Dermatol Surg.* 2009;35:429-435; discussion 435-436.

ADDRESS FOR CORRESPONDENCE

Gary D. Monheit MD
2100 16th Ave S
Suite 202
Birmingham, AL 35205-5067
Phone:.....(205) 933-0987
E-mail:.....monheitgd421@pol.net