

Neurotoxin Techniques for Men

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The number of men seeking botulinum toxin type A (BTX-A) has increased over the last decade. In addressing the needs of male cosmetic patients, clinicians cannot simply look to consensus statements and clinical trials for treatment guidelines when in fact the vast majority of clinical studies to date have been performed on predominantly female patient populations. This article discusses the reasons behind the recent demographic shift in the botulinum toxin market as well as the differences in perception of beauty across both genders. The available literature is reviewed to extrapolate and apply relevant data in the context of treating male patients. We also offer clinical pearls from our experience in a dermatology practice setting where the male cosmetic patient is strongly represented. Although there is no consensus on exact dosing regimens, as a general rule men require higher doses of all currently available neurotoxins. Furthermore, when evaluating male patients, clinicians must be cognizant of the Western ideals of male beauty while also taking into account each patient's specific muscle mass, muscle fiber pattern, and hair distribution pattern.

The vast majority of patients seeking noninvasive methods to reverse the signs of aging historically have been women, but men are now staking their claim in the neurotoxin market. Botulinum toxin type A (BTX-A) was the most popular noninvasive cosmetic procedure among men from 2008 to 2011, with twice as many men seeking this treatment since 2000.^{1,2} Moreover, there appears to be a demographic shift occurring in the botulinum toxin market. According to a report published by the American Society for Aesthetic Plastic Surgery, there has been a greater increase in the number of men seeking botulinum toxin injections from 1997 to 2010 than women.³ The

bulk of clinical studies have been performed on predominantly female patient populations. When the recommended doses and injection patterns from these studies are utilized in male facial musculature, male patients may be left undertreated or feminized. This article discusses the reasons behind the recent demographic shift in the botulinum toxin market as well as the differences in perception of beauty across both genders. We also offer clinical pearls on treatment of the male face with botulinum toxin injections.

THE MALE COSMETIC PATIENT

Both the scientific community and the laypress have developed theories to explain the demographic shift in the neurotoxin market. It is a well-established mainstream notion that there are noticeable social and economic advantages to being perceived as physically attractive. Numerous studies have shown that individuals who are perceived as "better looking" often have higher starting salaries and earn more money annually across various industries. Attractive individuals seem to generate more revenue than those who are considered unattractive.⁴⁻⁶ Moreover, studies have noted that attractive people report greater satisfaction with their lives than

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unattractive people.^{6,7} Despite federal laws such as the Older Workers Benefit Protection Act of 1990⁸ and the Age Discrimination in Employment Act of 1967,⁹ older individuals may be at a distinct disadvantage within the American labor market. Furthermore, modern American consumer culture and its resulting imagery seem to emphasize an obsession with youth. In his report on the psyche of the male cosmetic patient, Fried¹⁰ stated that men are motivated to seek aesthetic treatment based on socioeconomic advantages in the workplace from having a more youthful or attractive appearance. It also has been noted that many men are influenced by their female partners who are educated about cosmetic interventions such as Botox Cosmetic (Allergan, Inc), Dysport (Medicus Aesthetics, Inc), and Xeomin (Merz Aesthetics, Inc).¹¹⁻¹⁴ Some physicians such as Phillip Haeck, MD, president of the American Society of Plastic Surgeons, have suggested that the demographic change in the cosmetic procedure market may simply be a product of the nation's aging baby boomers.¹⁵ The proportion of men electing to undergo cosmetic procedures likely varies by location. In the last decade, we believe there have been definitive cultural shifts in Western society, especially notable on the coasts, with it now being more acceptable for men to be as concerned about their beauty and appearance as women.

WHAT MAKES A MAN ATTRACTIVE?

With an increasing number of men turning to cosmetic procedures such as neurotoxin injections to maintain an attractive and youthful appearance, it is reasonable to ask: What makes a man's face attractive? The study of facial aesthetics has origins that can be traced to a myriad of fields, including classical art, biology, psychology, anthropology, surgery, and orthodontics, to name a few. Scholars from Leonardo da Vinci to 21st century physicians have discussed the application of the mathematical ratio 1 to 1.618, also known as phi or the golden ratio, to describe the ideal proportions and angles of the human face. Other traits thought to be universally associated with health, beauty, and physical attractiveness of humans include symmetry, smooth complexion, averageness, and sexual dimorphism. Of particular relevance is the concept of sexual dimorphism and the notion that masculine facial characteristics are positively associated with male health and dominance.^{16,17} Specific features related to human sexual dimorphism are eyebrow size, jaw size, and eye size.¹⁸ In general, masculinity is associated with a wider face, a more prominent browridge, less space between the brows, and a well-defined jawline.¹⁹ Many male cosmetic patients hope to preserve these masculine traits when seeking treatment with neurotoxin injections. Although

our clinical experience validates these assumptions of aesthetic features, many ideals of beauty are subjective and differ across cultures and time. An awareness of the plurality of perspectives and an open discussion regarding each patient's individual preferences will help clinicians tailor cosmetic treatments and achieve good patient outcomes in today's increasingly diverse clinical settings.

HISTORY OF BTX-A

Botulinum toxin has been used for the treatment of hyperdynamic facial wrinkles since the early 1990s. An increasing body of evidence has supported the efficacy and safety of this cosmetic treatment. Botulinum toxins act by binding to presynaptic receptors on cholinergic nerve terminals, decreasing the release of acetylcholine and consequently preventing skeletal muscle contraction. Botulinum toxin type A and botulinum toxin type B are commercially available in a number of distinct preparations in the United States. Three BTX-A formulations currently are approved by the US Food and Drug Administration (FDA) for cosmetic indications.²⁰⁻²² Botox Cosmetic (hereafter referred to as Botox) is the original BTX-A product. Botox is composed of onabotulinumtoxinA and was FDA approved for treatment of glabellar lines in 2002. Dysport, which is formulated with abobotulinumtoxinA, was more recently approved by the FDA for the same indication in 2009. Xeomin, which is formulated with incobotulinumtoxinA, is the most recent BTX-A product to be approved for glabellar lines in the United States. Botox and Xeomin are available in 50- and 100-U vials, while Dysport is available in 300- and 500-U vials.²⁰⁻²²

BTX-A IN MEN

Analyzing cosmetic treatment techniques and appropriate doses of Botox, Dysport, and Xeomin is not a straightforward process. Direct comparisons of randomized controlled trials that investigate the effects of commercially available neurotoxins cannot be made because of variations in study design, injection patterns and volumes, and primary end points. The task of analyzing techniques specific to male patients is further complicated by the fact that most studies to date have been conducted on white female patient populations and small sample sizes. Nevertheless, drawing on extensive clinical experience and several lines of experimental evidence, experts appear to agree on a number of ways to approach treatment of the male cosmetic patient. The most widespread consensus is that men require higher doses of BTX-A than their female counterparts.^{23,24} This notion is predicated on the assumption that, in general, men have more skeletal muscle mass than women; typically, patients with more

muscle mass require more units of product per treatment area than patients who have thinner smaller muscles. Janssen et al²³ demonstrated that men have substantially more skeletal mass than women, both in absolute terms and relative to body mass. Moreover, studies indicate that androgen receptors may regulate signaling at this critical junction. Monks et al²⁶ hypothesized that these androgen receptors may regulate synapse-specific proteins that function to keep motor neurons alive. An expert on Botox, Flynn²⁴ postulated that men are subject to the hypertrophic effect of testosterone and therefore require higher doses of BTX-A. In our clinical practice, there have been a select number of patients who needed higher doses of Botox or Dysport while taking testosterone supplements to achieve the desired results. It may be relevant to ask patients if they are taking testosterone supplements prior to treatment or if they suddenly become resistant to treatment.

Glabella

Glabellar wrinkles typically appear when the corrugator supercilii, procerus, and orbicularis oculi muscles contract. Cosmetic treatment of the glabellar region with neurotoxins is FDA approved and extremely common among both men and women.

Dosing recommendations for Botox in men primarily are based on results from a dose-ranging study of exclusively male subjects conducted by Carruthers and Carruthers.²³ A randomized group of 80 men received a total dose of 20, 40, 60, or 80 U of Botox (n=20 for each) or a placebo administered to 7 intramuscular sites in the glabellar procerus complex. The investigators found that 40- to 80-U doses were effective and durable, while 20 U was inadequate for treatment of glabellar wrinkles in men. More specifically, only 65% of participants in the 20-U treatment group improved from severe to mild or none on the facial wrinkle scale. In the 40-, 60-, and 80-U groups, 90%, 95%, and 100% of participants, respectively, showed a similar response. Furthermore, a dose-response relationship was observed in the duration of effect on the facial wrinkle scale at attempted maximal contraction with a mean time to relapse of 17.6 weeks for the 20-U dose, 21.7 weeks for the 40-U dose, 22.8 weeks for the 60-U dose, and 24.2 weeks for the 80-U dose. The relapse rate was defined as a return to baseline value on the facial wrinkle scale at 2 consecutive study visits and by comparison with baseline photographs. The researchers concluded that the male glabella should be treated with a minimum of 40 U of Botox.²³ Results from this dose-ranging study confirmed prior clinical observations that men require higher treatment doses of BTX-A than women. Likewise, consensus papers and review articles suggest starting with doses of

approximately 40 U when treating the male glabella.²⁷ In our clinical practice, among a sample of 82 male patients treated with Botox in the last year, doses ranged from 10 to 65 U, with an average of 27 U for the glabella.

There currently are no dose-ranging studies that analyze the effects of Xeomin in the glabellar region. One German study by Imhof and Kühne²⁴ demonstrated the safety and efficacy of 20-U doses of Xeomin in the treatment of glabellar frown lines. A second large, head-to-head comparison study demonstrated the noninferiority of Xeomin to Botox in the treatment of glabellar wrinkles.²⁹ Although it targeted the crow's-feet and not the glabella, a split-face study conducted by Prager et al³⁰ compared the effects of equal doses of Xeomin and Botox and revealed a 1:1 dose-response relationship between the products. Using this ratio, one may extrapolate from the Carruthers and Carruthers²³ study from 2005 that men likely would benefit from a minimum 40 U of Xeomin administered to the glabella. Over the last year, we have used Xeomin for treatment of the glabella in a total of 10 male patients. Starting doses ranged from 12 to 54 U and averaged 28 U. It is important to note that the potency units of Xeomin are specific to the preparation and assay methods utilized. Although our clinical experience and the studies reviewed here support the use of a 1:1 dose-response relationship for convenience sake, units are not truly interchangeable with other preparations of botulinum toxin. The manufacturer makes it a point to warn practitioners against using a direct comparison or conversion ratio between products.²¹

Results from multiple efficacy and dose-ranging studies suggest that single 50-U doses of Dysport, administered equally among 5 intramuscular glabellar sites, are optimal for the treatment of frown lines.³¹⁻³³ However, 2 of these studies reported lower efficacy of 50-U doses of Dysport in men versus women.^{32,33} A fourth study confirms the notion that optimal dosing of Dysport varies considerably between genders.³⁴ In a sophisticated randomized controlled trial, Kane et al³⁴ compared the efficacy of variable doses of single Dysport treatments for moderate to severe glabellar lines. After 816 patients were randomized into Dysport and placebo treatment groups, the researchers further divided the experimental group based on gender and muscle mass. Women received doses of 50, 60, or 70 U, while men received doses of 60, 70, or 80 U, divided equally among 5 glabellar injection sites. They found that all doses of Dysport were efficacious compared with the placebo group, and they concluded that adjusting doses of Dysport based on gender and muscle mass provides greater and longer-lasting improvement of glabellar lines.³⁴ In our clinical practice, among a sample of 57 male Dysport patients treated in the last year, doses ranged from 15 to 95 U and averaged 51 U.

Regarding injection patterns in the glabella, a standard recommendation for all 3 commercially available products includes 5 intramuscular injection points for all patients.^{20,21} However, with respect to details such as additional injection points, there seems to be a lack of consensus among experts. In his review of Botox treatment and men, Flynn²⁴ remarked that the male corrugator supercilii "tend to have a rather broad course with the distal fibers of the muscle inserting into the skin far laterally." He emphasized the need to trace these fibers out to their later end point and place adequate doses into these fibers.²⁴ Alternatively, members of the Botox Consensus Group recommended a 7-point injection pattern, noting that the male muscular anatomy often calls for 2 additional bilateral injection points above the superior orbital rim.²⁷ Moreover, the panel noted that the total dose does not need to be divided equally among the 7 intramuscular sites. Specifically, they recommend injecting 20% of the total dose into the procerus muscle; 15% into both corrugator muscles; and 50% into the orbicularis oculi muscle, with 15% at each of 2 sites above the medial canthus and 10% at each of 2 sites above the midpupillary line.²⁷ Ironically, 2 small-scale studies comparing gender differences in facial musculature in cadavers suggested that the female procerus muscle is longer and variability in the location of the corrugator supercilii muscle was idiosyncratic rather than gender dependent.^{35,36} Larger studies comparing morphologic differences and facial musculature in the upper face in both genders are needed. In our own practice, we have used 5 to 6 injection points in the glabellar region depending on the individual patient's musculature, which is noted during examination.

Forehead

The treatment of the horizontal dynamic rhytides in the forehead is an off-label use of BTX-A in the United States. Among men, this treatment commonly is performed in conjunction with the treatment of the glabella, but it also is treated on its own. Not surprisingly, consensus papers note that "gender differences in muscle mass allow a higher starting dose in men."²⁷ Moreover, higher doses can be used in men because they often prefer a heavier, flatter, less arched brow; it also has been noted by experts that the frontalis is a "low-dose reactive muscle."²⁴ Because male patients, particularly those who are older, often use the frontalis muscle to increase their visual field, many complain of the forehead feeling heavy after receiving neurotoxin treatments in this area. A popular solution is to start treatment with a small dose and add more units on follow-up visits to avoid overtreatment in men.^{24,27} It also is important to carefully evaluate muscular bulk, the breadth and width of the frontalis muscle,

and the patient's hair pattern; in general, injection points are recommended below the hairline.

There are few studies that explore optimal dosing of BTX-A products in the forehead, and fewer that include male subjects. The Botox Consensus Group suggested starting with total doses of 20 to 30 U of Botox when treating the male forehead.²⁷ The group also recommended injecting 1- to 5-U aliquots per injection point, with higher doses for men. They also noted that dosage per injection point varied based on the number of injection points used. They recommended a range of 2 to 12 injection sites, with 4 to 6 being the most frequent number of injection sites used by panel members.²⁷ Following the assumption that Botox and Xeomin have a 1:1 dose-response relationship, similar doses and techniques can be used when treating the male forehead with Xeomin.^{29,30} Again, use of a simple conversion factor is not supported by manufacturers.^{20,21} In our clinical practice, among a sample of 61 male Botox patients treated in the last year, doses ranged from 8 to 47 U and averaged 22 U when treating the forehead. In the last year, we have treated 6 patients with Xeomin in the forehead with doses that ranged from 16 to 35 U and averaged 23 U. Consensus recommendations suggest a total dose range of 20 to 60 U of Dysport in male foreheads, with 2.5 to 10 U per injection point.^{37,38} Among the 62 male Dysport patients we treated in the last year, doses ranged from 10 to 75 U and averaged 45 U.

Some pearls and pitfalls are useful to consider when treating the male forehead. It is important to note that all injections should be made 1 to 2 cm above the orbital rim to prevent brow ptosis.²⁷ Moreover, experts agree that, more often than not, injection sites across the male forehead should form a straight line.³⁸ A common exception to this rule would be if male patients present with natural asymmetry. Classic anatomic depictions of the frontalis muscle indicate 2 bellies with a gap between them; however, the midline fibers of the frontalis muscle actually demonstrate considerable overlap in a substantial number of men. Consequently, it is wise to examine the contracted frontalis muscle to determine if central forehead injection points are necessary.²⁴ Many men also have androgenic alopecia and consequently present with hair loss or a receding hairline. In these patients, it is important to cautiously extend superior injection points high enough on the forehead.³⁹ Many men also require additional injection points in the lateral frontalis muscle to maintain a horizontal brow.

Brows

Treating the glabella and forehead in male and female patients can greatly affect brow shape. Although

specific to women, a study conducted by Carruthers and Carruthers⁴⁰ discussed the resulting effects on eyebrow height when treating the glabella with Botox. A retrospective analysis of patients' photographs from an older dose-ranging study showed that 20 to 40 U of Botox divided among 7 sites in the glabella produced significant variations in eyebrow position ($P < .05$). The researchers theorized that these changes were due to partial inactivation of the medial frontalis, with increased muscle tone in the lateral frontalis.⁴⁰ In practice, such an effect creates an arched brow that often is perceived as too feminine for a male patient. In our clinical experience, most men prefer to have a straight prominent brow because of its association with masculinity. This observation is consistent with anatomic studies that demonstrate the male brow is flatter with less contour and sits lower along the orbital rim compared with the female brow.^{41,42} Additionally, it has been observed that men have more prominent and fuller lateral brows as well as fuller upper eyelids.^{41,42} Given these circumstances, clinicians who perform glabellar treatments risk feminizing their male patients if the position of the male eyebrow becomes overlifted or the arc of curvature becomes too prominent. Many experienced clinicians have offered their expertise on how to correct this effect, including Flynn²⁴ and the Botox Consensus Group.²⁷ We recommend injecting 0.5 to 1 U of Botox or Xeomin or 1 to 4 U of Dysport approximately 1 cm above each lateral brow to prevent an overarched appearance. Certain patients benefit from having these additional units distributed over 2 to 3 injection points along the lateral frontalis muscle. In our clinical practice, 67% of 149 men who have had glabellar treatments also have undergone treatment of the lateral frontalis muscle.

Crow's-feet

Another common cosmetic use of BTX-A is the treatment of periorbital rhytides. A standard technique includes 3 injection sites overlying the lateral fibers of the orbicularis oculi muscle on the lateral aspect of each orbital rim. As with other regions of the face, randomized controlled trials analyzing dosing in the periorbital area predominantly have been conducted on female patient populations.

Results from a dose-ranging study conducted by Lowe et al⁴³ suggested that 12 U of Botox per side is an optimal dose for both men and women (ie, 4 U per injection site); however, consensus papers recommend higher doses ranging from 12 to 16 U of Botox per side when treating crow's-feet in men.^{27,44-46} In the last year, we have treated 48 men with Botox for crow's-feet. Doses ranged from 4 to 23 U and averaged 13 U per side. Dosing recommendations for Xeomin currently are based on a

German comparison study conducted by Prager et al.³⁰ Results from this split-face study comparing Botox with Xeomin in the treatment of periorbital lines or crow's-feet confirmed the suspected 1:1 dose ratio. Among the 4 male Xeomin patients we have treated in the past year, crow's-feet doses ranged from 4 to 12 U and averaged 9 U per side. A third dose-ranging study by Ascher et al⁴⁷ shed light on optimal dosing of Dysport in the crow's-feet area. The authors of this double-blind, placebo-controlled study demonstrated that 30- and 45-U doses of Dysport were more durable than 15-U doses divided equally among 3 intramuscular injection sites per eye. Although recommendations are not specific to men, consensus papers recommend a total of 15 to 40 U of Dysport per side, or 5 to 13 U per injection.^{37,38,46} In our clinical practice, a sample size of 42 male patients in the last year yielded Dysport doses that ranged from 5 to 39 U and averaged 29 U per side for crow's-feet. We also commonly inject into the inferior palpebral portion of the orbicularis oculi muscle, just beneath the lower lash line. Clinically acceptable doses are 0.5 to 1 U of Botox or Xeomin and 1 to 4 U of Dysport.

Lower Face

In our experience, requests for cosmetic treatment of the lower face are infrequent among men. In our sample, only 1 of 161 (0.62%) men requested treatment in this area. Consequently, we have chosen not to focus on the use of neurotoxins in the lower face.

SIDE EFFECTS

Many men process the pain and anxiety associated with cosmetic procedures differently than their female counterparts. Although men in general are more tolerant of pain than women, pain in the context of a cosmetic procedure presents a unique set of circumstances and often is handled differently than other sources of pain.^{48,49} Consequently, men often are less familiar with and more anxious about pain during cosmetic procedures³⁹; many men are even more anxious about the visual signs and side effects of cosmetic procedures. Bruising is a concern for men, as many men take antiplatelet agents and blood thinners such as warfarin sodium, nonsteroidal anti-inflammatory drugs, and fish oil for cardiovascular management. Regardless of their likelihood for bruising, the issue of camouflaging a bruise also is more challenging in men; although women feel comfortable using makeup to conceal bruises, most men are not open to this option. Special skin camouflaging products specifically designed to cover skin conditions are available, which we find to be more acceptable among male cosmetic patients. Another alternative is treatment with agents intended

to speed the resolution of an ecchymosis, such as arnica or bromelain.^{50,51}

CONCLUSION

More men are seeking neurotoxin treatments each year and will probably continue to seek more of these noninvasive treatments as our culture becomes more accepting of the concept of male beauty. There is no consensus on exact dosing regimens, but as a general rule, men require higher doses of all currently available neurotoxins. When evaluating male patients, it is important to be cognizant of the Western ideals of male beauty while taking into account the patient's specific musculature and personal preferences.

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