Cosmetic Use of AbobotulinumtoxinA in Men: Considerations Regarding Anatomical Differences and Product Characteristics

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ABSTRACT

The proportion of men seeking facial rejuvenation with botulinum neurotoxin type A (BoNTA) products is increasing. The number of male patients treated in the 5-year period between 2009 and 2014 grew by 25%. There is little clinical data supporting gender-specific efficacy with regard to dosing and injection placement in men. To nurture the confidence associated with treatment of male patients, clinicians are in need of more informational materials to develop their evaluation and treatment strategies. Three BoNTA products are currently available in the United States (US) for treatment of the upper face. The varying potency of the different BoNTA formulations is reflected by disparate dose-response characteristics, meaning they are not interchangeable for injection purposes. Clinicians who are familiar with the characteristics of all the BoNTA options will be equipped with the necessary tools to provide their male patients with a desired outcome.

Among the product options available in the US, Dysport® (abobotulinumtoxinA) (Galderma Laboratories, L.P., Fort Worth, Texas) is unique in that its recommendations for reconstitution provide the clinician with 2 different final product concentrations. The flexibility provided by a variable dose may be a valuable tool for tailoring treatments to male patient-specific needs, which may include a more conservative outcome, maintaining a certain degree of muscle activity and expressivity. Achieving a conservative outcome may be the key to a positive experience for the male patient.

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INTRODUCTION

The cosmetic use of botulinum neurotoxin type A (BoNTA) for facial rejuvenation is desirable because the treatment procedure is minimally-invasive, the effects of BoNTA are relatively fast-acting, and the procedure involves little or no patient down-time. Since 2000, BoNTA's growth trend is reflected in a 748% increase in procedures performed in the US, and has consistently remained the most frequently performed procedure in the American Society of Plastic Surgeons (ASPS) category of minimally-invasive cosmetic procedure performed for over a decade.[1,2] Men have consistently remained a smaller proportion of the patients seeking BoNTA procedures (approximately 6%), but the true number of male patients is actually substantial. The male statistic alone is reflected by a 25% increase in BoNTA procedures performed between 2009 (307,649) and 2014 (410,913).[3,4] In this light, the true need for treatment strategies tailored to the male patient has become evident for cosmetic dermatologists and plastic surgeons.

Clinical data evaluating the gender-specific differences regarding safety, efficacy, and dosing for BoNTA treatment of the male patient are limited.[5] In addition, development of this knowledge through practical experience can be a challenge, since men are still only a small portion of most clinician's total patient population. The current techniques and safety considerations in place for female patients can be used as guidelines for male patients, but the cosmetic outcome for the male patients must take into account the gender-specific anatomical differences. The anatomical features that distinguish the male face should be foundational in the patient evaluation process, as well as in the treatment design to deliver desirable outcomes.

Dysport® (abobotulinumtoxinA) (Galderma Laboratories, L.P., Fort Worth, TX) is a BoNTA indicated for cosmetic use in adult patients younger than 65 years of age to temporarily improve the appearance of moderate to severe dynamic facial wrinkles (glabellar lines) produced by the underlying activity of the procerus and corrugator muscles.[6] Intramuscular injection of BoNTA decreases muscle contractibility by blocking the release of acetylcholine within neuromuscular junctions.[6,7]

AbobotulinumtoxinA was approved by the US Food and Drug Administration in 2009 as the second of 3 BoNTAs approved for cosmetic use in the US, which also includes Botox® Cosmetic (onabotulinumtoxinA) (Allergan, Inc, Irvine, CA), approved in

2002; and Xeomin® (incobotulinumtoxinA) (Merz Pharmaceutical, Frankfurt, Germany), approved in 2010.[6,8,9] Although all the cosmetic BoNTA products act on the same neurotransmitter, they each have distinct formulation differences that influence product reconstitution and dosing guidelines. The abobotulinumtoxinA formulation is notably different from the other BoNTA formulations and has distinctly different guidelines for calculation of product reconstitution and dosing.

There are currently no BoNTA manufacturer recommendations for specific injection points that are defined by male facial anatomy. The knowledge gap is resonated by review articles that highlight the rationale for male-specific evaluation and treatment; and there is also clinical evidence that dosing guidelines should vary by gender for optimal clinical effect.[10-12] This review is intended to provide a combination of useful information for adapting injection techniques to the male patient. The review content touches on current BoNTA dosing guidelines, gender-specific anatomical differences, clinical data that support variable dosing in male subjects, and valuable pearls of knowledge provided by the contributing authors. For clinicians who want to gain confidence in meeting the needs of the male patient and proficiency using all available BoNTA options, this overview may represent a source of helpful information.

Notable Differences Between Botulinum Neurotoxin Type A Products

The potency of the different BoNTA formulations is specific to their individual manufacturing processes; therefore, product reconstitution and dose-response characteristic associated with each formulation are not interchangeable with respect to clinical efficacy.[6,8,9,13]

Product Reconstitution and Final Concentration

BoNTA products are reconstituted in a range of final concentrations. The abobotulinumtoxinA cosmetic product is provided as a 300 unit (U) vial (also referred to as Speywood Units) with 2 recommended reconstitution volumes of 1.5 mL and 2.5 mL, for final concentrations equal to 10 U per 0.05 mL (20 U per 0.1 mL) and 10 U per 0.08 mL (12 U per 0.1 mL), respectively.[6] Alternately, the onabotulinumtoxinA and incobotulinumtoxinA products are provided in 2 different vial sizes for cosmetic indications. Both products are available as either a 50 U or 100 U vial, which are reconstituted to total volumes of 1.25 mL and 2.5 mL, respectively, resulting in a final concentration equal to 4 U per 0.1 mL volume.[8,9] (Table 1).

Total Dosing Concentration Per Indicated Treatment Area

According to the product information recommendations, the injection dose for abobotulinumtoxinA is 50 U (0.25 mL) total, divided equally (10 U/0.05 mL) among 5 injection points in the glabellar region, administered by 2 in each corrugator muscle and 1 in the procerus muscle. Alternately, the recommended

TABLE 1.

Recommended Reconstitution Volumes for Botulinum Neurotoxin Type A

BoNTA U/Vial	Total Vial Reconstitution			
	1.25 mL	1.5 mL	2.5 mL	3.0 mL
	Resulting Dose/Volume			
abobotulinumtoxinA				
300		10 U/0.05 mL (20 U/0.1 mL)	10 U/0.08 mL (12 U/0.1 mL)	10 U/0.1 mL
onobotulinumtoxinA				
50	4 U/0.1 mL			
100			4 U/0.1 mL	
incobotulinumtoxinA				
50	4 U/0.1 mL		2 U/0.1 mL	
100	8 U/0.1 mL		4 U/0.1 mL	

injection dose for onabotulinumtoxinA and incobotulinumtoxinA is 20 U (0.5 mL) total; divided equally among 5 injection points (0.1 mL/injection point) in the glabellar region, administered by 2 in each corrugator muscle and 1 in the procerus muscle. Recently, an additional indication approved for onabotulinumtoxinA in the treatment of lateral canthal lines (crow's feet) recommended as 24 U (0.6 mL) total, divided equally among 3 injection points (4 U/0.1 mL) per side of the face (6 injections total).[8]

Botulinum Neurotoxin Type A Conversion Ratios

Understanding the dose conversions between each BoNTA product is critical to successfully incorporating them into practice. As mentioned, the dose-response equivalence between BoNTA products cannot be standardized due to differences in their manufacturing processes. These differences are reflected the accepted range of potency between products as ± 20% to 25%, established by European Pharmacopoeia.[14]

Approximate dose conversions have been studied, and provide a helpful precedent for clinicians who wish to develop confidence in the BoNTA dose response of products they may not be familiar with. A conversion ratio of approximately 2.5:1 (50 U abobotulinumtoxinA to 20 U onabotulinumtoxinA) has been clinically supported and widely accepted.[14-17] A review of the experimental studies using the extensor digitorum brevis test, facial lines, and anhidrotic action halo tests support dose-conversion ratios less than 3:1.[18] Ratios higher than 3:1 in non-facial muscles, such as those associated with cervical dystonia and palmar and primary axillary hyperhidrosis, have demonstrated greater efficacy with abobotulinumtoxinA; however, a caveat for using these studies as a basis for treatment of facial muscles may not be an appropriate equivalent, since facial muscles have a greater distribution of BoNTA target neuromuscular junctions compared with larger muscles of the body.[19-22]

The field of effect (also known as "diffusion halo") associated with the different BoNTAs has been historically misinterpreted as a variable parameter among products; however, it has since been clarified that field of effect among BoNTAs is actually comparable when equipotent doses are being compared (isovolumetric injections of the same labeled unit dose).[23] Only at ratios higher than 3:1 (abobotulinumtoxinA to onabotulinumtoxinA) is the abobotulinumtoxinA field of effect greater than onabotulinumtoxinA, which clearly demonstrates that the field of effect is a function of the actual dose and not of the product characteristics.[24-27]

Considerations for Botulinum Neurotoxin Type A Variable Dosing in Male Patients

None of the BoNTAs are approved for variable dosing beyond the instructions provided in the product prescribing information; however, a tailored dosing technique may help achieve a desired outcome. Moreover, a strong rationale for variable dosing is that facial muscle mass, injection sites, and depth will differ between individuals and between genders.[28] Clinical data resources available to clinicians who want the evidence-based results regarding treatment of their male patients are unfortunately limited to a small number of studies.

Clinical Trial Data

At the time of this overview, 17 pivotal clinical studies evaluating the use of BoNTA products in the cosmetic treatment of the moderate to severe dynamic wrinkles in the upper face have presently been identified using a PubMed search.[11,12,29-44] Collectively, a total of 705 male subjects (treatment and placebo) have participated in these studies. However, male subgroup analyses and gender-specific dosing adjustments were only conducted in 2 of those studies.[11,12] The subgroup analysis, performed on 15 male and 90 female subjects, involved intramuscular injections in the glabellar region at 5 distinct sites, with equivalent portions of a total dose equal to 10 U abobotulinumtoxinA per 0.05mL.[11] The results demonstrated that 93% of female subjects, compared with only 67% of male subjects, experienced significant reduction in glabellar line severity scoring resulting from a single 50 U dose. The investigators concluded that the lower percentage of male subjects demonstrating significant reduction in line severity was due to the greater muscle mass of the male glabellar region, and that treatment of the male glabellar region may require more than a 50 U dose.

This conclusion was further supported by a separate evaluation of the abobotulinumtoxinA dose-response in men vs women (based on muscle mass rating) for the treatment of glabellar lines.[12] In this randomized, double-blinded, placebo-controlled study, 97 male subjects received 5 intramuscular injections with equivalent portions of a total dose equal to 60 U, 70 U, or 80 U in a total volume of 0.5 mL to 0.7 mL. Alternately, 715 female subjects received equivalent portions of the total dose administered as 50 U, 60 U, or 70 U in a total volume of 0.4 mL to 0.6 mL (10 U less than males with similar muscle mass). The study's findings demonstrated that the response rate for men, although still lower than that for women, was higher than that seen in studies using a 50 U dose. Both studies also concluded that a higher total dose of BoNTA was not associated with an increase in adverse events.

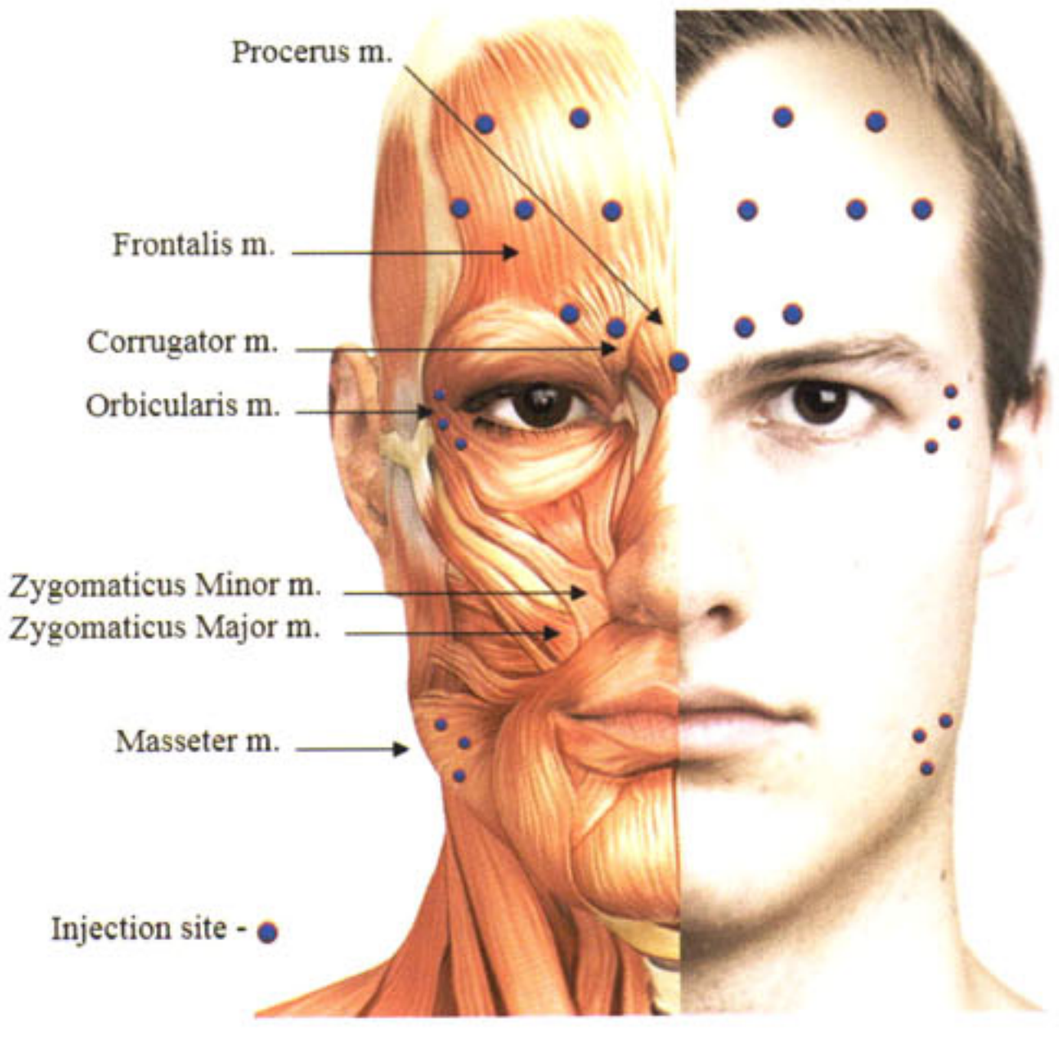
Facial Anatomy Affecting Male Vs Female Treatment Objectives

There are a number of key physiological differences between male and female facial features. Although men and women may have soft-tissue facial structures of comparable shape, men have a greater craniofacial size and greater magnitude of soft-tissue displacement during mimetic muscle movement.[45,46] For both men and women, the elastic mechanical properties of the skin decline with aging; however, men tend to have more severe facial wrinkles than women.[47,48]

Treatment of the Glabellar and Upper Forehead Wrinkles

The eyebrow depressor muscles are made up of the procerus, the corrugator supercilii, and the depressor supercilii (Figure 1). Together, the activity of these muscles depresses the brow downward and medially. This activity, reflected by squinting and frowning, contributes to the dynamic wrinkles of the glabellar region. The 5-point injection pattern should be at least 1 cm above the upper orbital rims and positioned medial to the mid-pupillary lines (Figure 1).[49] However, the injection pattern for men may require a wider extending pattern to account for a greater muscle mass and lateral extension of the glabellar muscles.[28,50]

FIGURE 1. Facial muscle anatomy and injection patterns for the male face.



The procerus muscle originates in the tendons close to the nasal bone and extends vertically to the frontalis muscles above the brow.[28] The depressor supercilii, which are parallel to the procerus, originate near the canthus and extend vertically into the brow.[51] Treatment of the procerus requires a single injection placed carefully to avoid the transition zone with the medial portion of the frontalis. An injection point too close to the medial frontalis will contribute to elevation of the lateral brow when the frontalis muscle contracts.[49] It has been suggested that injection of the procerus can be followed by light massage directed in a lateral-focused movement to facilitate spread of the product into the depressor supercilii portion of the corrugator.

The corrugator supercilii originate near the medial brow bone on either side of the central procerus, and extend laterally along the orbital ridge.[28,52] The male supraorbital ridges are more prominent and, medially, transition more evenly into the glabella region, which also has a greater projection.[53,54] The corrugator supercilii muscle may extend more laterally in men than women. Contributing authors suggest that a helpful landmark for location of an appropriate injection point is to identify the lateral aspect of the corrugator muscle and where it dimples or inserts into the skin, evident when the patient frowns. Treating just medial to its insertion point (and knowing that this may be more laterally based in men) will help aid in achieving the best results.[49] Failure to place the injection far enough laterally may allow contractibility at the distal portion of the muscle, producing an unnatural effect.

Another use of BoNTA, and an important consideration for the male patient, is treatment of the frontalis muscle (Figure 1).[24,55,56] The frontalis muscle is the only elevating muscle of the eyebrow and has no bony attachments. Rather, it shares blended medial muscle fibers with the procerus, and blended central and lateral fibers with the corrugator and inner orbicularis oculi muscles, respectively. When the depressor muscles of the brow area are treated with BoNTA, the contraction of the frontalis will be unopposed and pull up on the eyebrow.

The male eyebrow sits lower on the orbital rim than a female's and, perhaps because of this, male eyebrow position also tends to appear flatter and in a more horizontal alignment. To maintain a natural brow position, a horizontal injection pattern in the lower portion of the frontalis muscle that is approximately 1 cm to 2 cm above the orbital rim to avoid brow ptosis is recommended by contributing authors (Figure 1). In addition, treatment of the lateral portion of the frontalis is also recommended to prevent contraction of the lateral frontalis, which can exaggerate an arching of the outer eyebrow.[49] Treatment of the lateral frontalis muscles combined with treatment of the glabellar complex is a crucial aspect of maintaining the flat male brow. If the glabellar complex is injected with BoNTA without any treatment of the frontalis, the unopposed elevating activity of the lateral frontalis can lift the outer edge of the brow and, while this may be a desirable outcome for female patients, it may produce a feminizing peaked appearance of the male brow.

The treatment of horizontal forehead lines is also off-label use of BoNTA, but is commonly used for both males and females, and does not necessarily have to be treated in combination with the glabellar region.[24,55,56] The consensus recommendations for injection placement for horizontal forehead lines is a total of 4 to 6 points (possibly 8) arranged in a straight line in 1 or more rows depending on the height of the hairline for male patients, and the lateral-most points should be aligned with the external orbital rim.[49,50]

For a male patient with a receding hairline, the injection sites will need to extend higher and further into the scalp area to prevent an unnatural look of the wrinkling in the scalp area where the frontalis is still able to fully contract.[5,57] In general, the greater surface area of the male frontalis requires a wider and higher injection pattern in comparison to what is used in women (Figure 1). It is suggested that the biggest differences in treatment of the upper face in male vs female patients are the potential need for a higher dose to achieve clinical results and use of a flatter frontalis injection pattern. For women, the injection pattern may resemble a "V' or "gull in flight" shape, but for men this dose pattern should be flatter and extending into the "power alleys" (corners of the hairline) for men with receding hairline.

Treatment of Periocular Rhytides

The orbicularis oculi muscle is a broad circular muscle divided into 3 portions, the lacrimal, the palpebral, and the orbital portions. The inner lacrimal and palpebral portions control the involuntary blinking of the eyelids, while the outer orbital portion of the muscle (pars orbicularis) encircling the orbit is subject to voluntary control (Figure 1).[49] In men, the outer orbicularis muscle may be broader and more expansive and a greater activation of cheek elevator muscles (zygomatici) translates into a greater lateral fanning of periocular wrinkles (crow's feet lines).[46,58] In addition, cutaneous aging in men results in a greater degree of lower eyelid sagging than in women.[59]

The international consensus recommendations for the treatment of crow's feet lines with abobotulinumtoxinA is an injection of 6 points (3 points per eye), with 5 U to 10 U/injection point placed at the lateral part of the orbicularis oculi and about 1 cm to 2 cm from the external orbital rim.[49] A modified injection pattern based on these recommendations has also been described in an onabotulinumtoxinA clinical trial in male (13.1%) and female (86.9%) subjects.[60]

Two injection patterns were defined in this study, which included a series of 3 injection sites. The first injection was in the

orbicularis oculi at the level of the lateral canthus, at least 1.5 cm to 2.0 cm temporal to the lateral canthus and just temporal to the lateral orbital rim. The second injection was placed 1 cm to 1.5 cm above the first injection site (with an approximate 30-degree angle medially). The third injection was placed 1 cm to 1.5 cm below the first at an approximate 30-degree angle medially. Alternatively, as a second option when the crow's feet lines were primarily below the lateral canthus, the first injection site could be placed just below the lateral canthus. Furthermore, the line of injection sites were angled from anteroinferior to superoposterior. The most anterior injection was placed lateral to a line drawn vertically from the lateral canthus, and the most inferior injection site was superior to the maxillary prominence. The elevating activity of the frontalis is also a consideration with the superior injection point for crow's feet, which can be moved inferiorly in men or avoided altogether as it may contribute to lateral brow elevation and an arched brow appearance.

More injection points may be required for the male's outer orbicularis than for the female's to accommodate the further lateral reach of the muscle. Crow's feet lines in men usually have more of an inferior fanning pattern due to the contraction of both the orbicularis oculus and zygomaticus muscles.[61] Therefore the injection site is lower and often near the insertion site of the zygomaticus.[49,62] Importantly, the injection point should be placed to avoid the zygomaticus since its contraction is necessary to elevate the cheek and corners of the of the mouth. Contributing authors suggest using superficial microinjections for the lateral inferior orbicularis, which may otherwise risk affecting the zygomaticus with a deeper injection. Although treatment of periocular wrinkles is considered "off label" for some BoNTA products, it is frequently requested and performed by clinicians.[49,63]

Lower Face

With regard to the lower face, men generally have a more prominent jawline with a larger and wider chin area that also has a greater forward projection in comparison to women.[64] The masseter muscle at the outer corners of the jaw contribute greatly to the masculine contour of a man's lower face (Figure 1). Although treatment of the masseter muscle in the male patient may potentially feminize the contour of the jaw, there may be aesthetic benefit for male patients with asymmetric or aesthetically detracting prominence of the lower face contour due to the masseter muscle.[50,65] The injection placement in the masseter is dependent on the number of bulges present while the jaw is being clenched. Placement of the primary injection is recommended for the most prominent bulge of the masseter. Further injection points (1 to 3) can be used depending on the degree of hypertrophy; mono, double, triple, or excessive.[65]

The consensus recommendations on injection depth and placement include 3 injections per side (6 total) using a perpendicular injection technique inserted to a depth equivalent to the middle third of the needle.[66] The doses established for cosmetic reduction of masseteric mass have been determined primarily in female patients, but the dose needed, regardless of gender, is dependent on the muscle thickness, an attribute which may vary among patient ethnicity and gender.[67-69] In East Asian female patients, a total dose of 100 U to 140 U abobotulinumtoxinA for each side was based on muscle thickness (ranging from 100 U for 10 mm muscle thickness to 140 U for 16 mm muscle thickness) was found to be most effective.[67] The injections were divided equally among 3 to 4 injection sites depending on width of the muscle (following the contour line of the mandible). In Brazilian female patients, a total dose of 90 U abobotulinumtoxinA, divided equally among 3 injections for each side, was found most effective.[69]

The area for injection was established by drawing a line from the mouth angle to the lower implantation of the ear, and outlining the anterior and posterior edges of the muscle with the ramus of the mandible as the lower border of the area. The injections were applied first at an upper central point followed by another 2 at lateral points 1 cm away from the initial point. In Western female patients, a total dose of 25 U to 30 U of onabotulinumtoxinA for each side was found most effective.[68] The area for injection was established by drawing a line from the external auditory meatus to the middle of the philtral column, and outlining the anterior and posterior borders of the muscle. Within that area, 5 injections (in a pattern equivalent to 2 upper, 2 lower, and 1 central) were placed in the lower half of the muscle, and at least 1cm from the muscle border. The cosmetic improvement lasted between 9 and 12 months. It also noteworthy to inform patients that it may take at least 6 months for optimal results to appear for treatment of masseter hypertrophy. Furthermore, it may take up to a year to notice significant recontouring, and retreatments are suggested at 3- to 4-month intervals.[63]

Expectations of the Male Patient

Aesthetic treatments of the male face have gained increasing social acceptability, and men may feel a greater sense of societal permission than ever before to seek treatment. Individual motives for the pursuit of cosmetic treatment may vary markedly between men and women, such as a more youthful appearance to gain advantage in a competitive work place vs a woman's motive for a more youthful appearance to promote body image and self-esteem.[70] Men also have different aesthetic standards and goals than women. While women often wish to discuss the rationale and emotional impetus for cosmetic work during a consultation, men may be more inclined to stay focused on seeking a solution to an immediate problem. Men may also desire more subtle changes that are not necessarily recognizable by peers. The male patient may primarily want a conservative approach, and only want to soften the deepest dynamic wrinkles, while still maintain expressivity. Men also

tend to prefer fast procedures with no downtime. In the event of follow-up treatments, clinicians may have to manage their expectations and tolerance for additional treatments necessary to achieve optimal results.

SUMMARY

Clearly, the evidence-based results supporting the use of BoNTA in male facial cosmetic treatments lag far behind the apparent demand reflected by the ASPS report on consumer preference. The male cosmetic patient is the new kid on the block, and it may be the clinician's responsibility to help nurture this developing patient demographic. The techniques and safety considerations used for female patients are adequate guidelines for male patients, but the gender-specific differences in anatomy are foundational in the patient evaluation process, injection patterns, and dosage requirements necessary for male patients. Clinicians who are familiar with the characteristics of all the BoNTA options will be the best equipped with the necessary tools to provide their male patients with a desired outcome.

Undeniably, a clinician's confidence regarding preparation of a final concentration is essential for appropriate injection volume and dose. Clinicians who want to make the most informed product choice, which best suits the particular injection strategy, will need to review all product recommendations. The utility of abobotulinumtoxinA in helping the clinician achieve a variable dose, while using the same incremental volume during an injection, will facilitate a more conservative male patient-specific treatment outcome.

In the immediate future, the clinician's goal should be to recognize the gender differences, even subtle ones, which may ultimately enhance the male patient's experience and improve results. A conservative approach to injection dosing, involving follow-up treatment, may be a helpful management strategy for determining initial patient-specific dosing in men. An added advantage to this approach is that lower doses, in combination with an injection pattern that doesn't risk altering the brow line, will also facilitate retention of natural muscle movement and may help ensure a positive experience for the patient.

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Dr. Bloom is a paid consultant, speaker, and trainer for Galderma's promotional programs, and also a clinical investigator for Galderma. Dr. Green is a paid consultant and clinical investigator for Galderma. Dr. Bowe is a paid consultant and trainer for Galderma. Erika von Grote and Dr. Nogueira are employees of Galderma Laboratories, L.P.

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