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# The association between age and long term cosmetic effect of treatment with botulinum toxin

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**THE ASSOCIATION BETWEEN AGE AND LONG TERM  
COSMETIC EFFECT OF TREATMENT WITH BOTULINUM TOXIN**

by

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B.S., University of Virginia, 2012

Submitted in partial fulfillment of the  
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Master of Science

2016



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**KELSEY COX**

**ABSTRACT**

Cosmetic treatment with botulinum toxin type A injections is the top non-surgical cosmetic procedure in the U.S. Many patients are beginning treatment at a younger age to prevent the development of facial wrinkles associated with aging. However, there is limited data to support the use of prophylactic botulinum toxin injections. Patients beginning treatment at a younger age have fewer wrinkles requiring fewer units to treat, which reduces the overall cost of treatment. Patients also maintain higher levels of self-esteem by preventing or delaying the onset of facial wrinkles that can negatively impact their appearance. This study proposes that patients receiving botulinum toxin injections at a younger age (< 35) will have higher satisfaction with treatment outcomes. By demonstrating an association between starting age of injections and patient satisfaction, this study aims to provide merit for clinical trials studying the effectiveness of prophylactic botulinum toxin injections for cosmetic indications.

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## **LIST OF ABBREVIATIONS**

BMC .....	Boston Medical Center
BTA .....	Botulinum toxin type A
SNAP-25 .....	Synaptosomal-associated protein of 25 kDA

## **INTRODUCTION**

### **Background**

Imprinted facial lines are the permanent lines that develop on a face after years of repeated muscle contractions causing dermal and epidermal breakdown.<sup>1</sup> These lines, specifically horizontal forehead lines and vertical glabella (“11’s”) make one appear aged, tired, or angry.<sup>2</sup> Decreasing the intensity of these lines and preventing imprinting with botulinum toxin has become a common office procedure in the field of cosmetic medicine. Many providers and patients endorse benefits of starting treatments with botulinum toxin before facial lines initially appear.

Botulinum toxin is part of the cosmetic injectable class known as neuromodulators. The toxin blocks the release of acetylcholine from presynaptic nerve terminals into the neuromuscular junction, thereby preventing muscle contraction.<sup>2</sup> Cosmetic treatment with botulinum toxin causes intentional, sub-acute paralysis of muscles responsible for the development of facial lines. The rationale behind facial line prevention with botulinum toxin is that if the muscles are unable to make repeated contractions, then the resulting lines will not form, leaving the patient free of the undesired appearance mentioned above.

### **Statement of the Problem**

Currently, there is no substantial evidence supporting the benefits of wrinkle prophylaxis with botulinum toxin, but patients are asking the question of “When is too early to start?”<sup>1</sup> The only research documenting an early initiation of BTA treatment was a retrospective twin study in 2006.<sup>2</sup> While the twin that started in her 20s had fewer facial



lines after 13 years of consecutive treatments, the other twin only had two treatments four years apart in her 30s. It is unknown if the second would have equal results and satisfaction if she started later, but continued with consecutive treatments.

Early treatment equates to higher costs and more office visits over one's lifetime, but patients are beginning treatments earlier despite the lack of evidence demonstrating the cost-effectiveness of wrinkle prophylaxis with BTA. These patients are likely satisfied with their treatment as the number of BTA procedures continues to increase and remains the most popular non-invasive aesthetic treatment in the United States.<sup>3</sup>

Multiple studies have demonstrated that satisfaction with BTA treatment is high, but none have looked at satisfaction rates based on starting age.<sup>4</sup> It was noted in clinical trials that BTA injections were more effective and lasted longer in younger vs. older patients, which would likely lead to higher rates of satisfaction, but this has yet to be demonstrated.<sup>5</sup>

## **Hypothesis**

If botulinum toxin treatments are received at a younger age (< 35), then there will higher patient satisfaction with treatment outcomes.

## **Objectives and specific aims**

Many patients begin treatment with botulinum toxin at an early age for wrinkle prevention by initiating therapy before facial lines develop. This study proposes to further explore the association between age at initiation of cosmetic treatments with botulinum toxin and patient satisfaction with treatment outcomes. Improved satisfaction in the group

receiving treatments at an earlier age could implicate further studies regarding prophylactic botulinum toxin treatment.

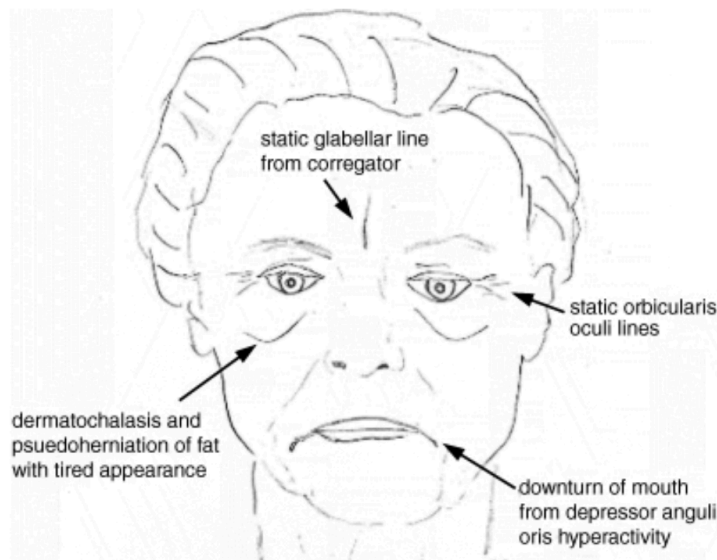
- To determine the relationship between younger starting age ( $< 35$ ) of botulinum toxin treatments, patient satisfaction rates, and treatment outcomes using the Facial Lines Treatment Satisfaction Questionnaire

## **REVIEW OF THE LITERATURE**

### **Overview**

The human face provides a universal method of communication as well as a expressing an individual's health, emotion, and age.<sup>6</sup> It also presents a level of physical attractiveness that has social implications impacting the individual's well-being.<sup>7</sup> As the face ages, bone atrophy and loss of skin elasticity accelerate the appearance of wrinkles formed by repetitive contractions of the face.<sup>8</sup> Even though they are not pathologic, these wrinkles become permanent, even at rest, and may have a significant effect on a person's communication, attractiveness, and self-esteem.<sup>7</sup> Botulinum toxin type A (BTA) injections have the ability to alleviate these negative effects associated with facial aging.

Facial expression is an integral part of verbal and non-verbal communication. The lines associated with aging portray facial miscues that incorrectly signal an emotion that is not felt. A depressed and furrowed brow signals that the person is worried, angered, or displeased. Brow depression and sagging eyelids portrays drowsiness or exhaustion. Sagging and down-turned corners of the mouth create an appearance of sadness or displeasure. Just a single glabellar crease may be interpreted as anxiety or irritation. These features are observed at rest as the face ages and give's the individual a negative expression at baseline (Figure 1).<sup>7</sup>



**Figure 1. Miscues of the aging face. Subject is cheerful and happy, but face projects affect of being tired, angry, and sad.<sup>7</sup>**

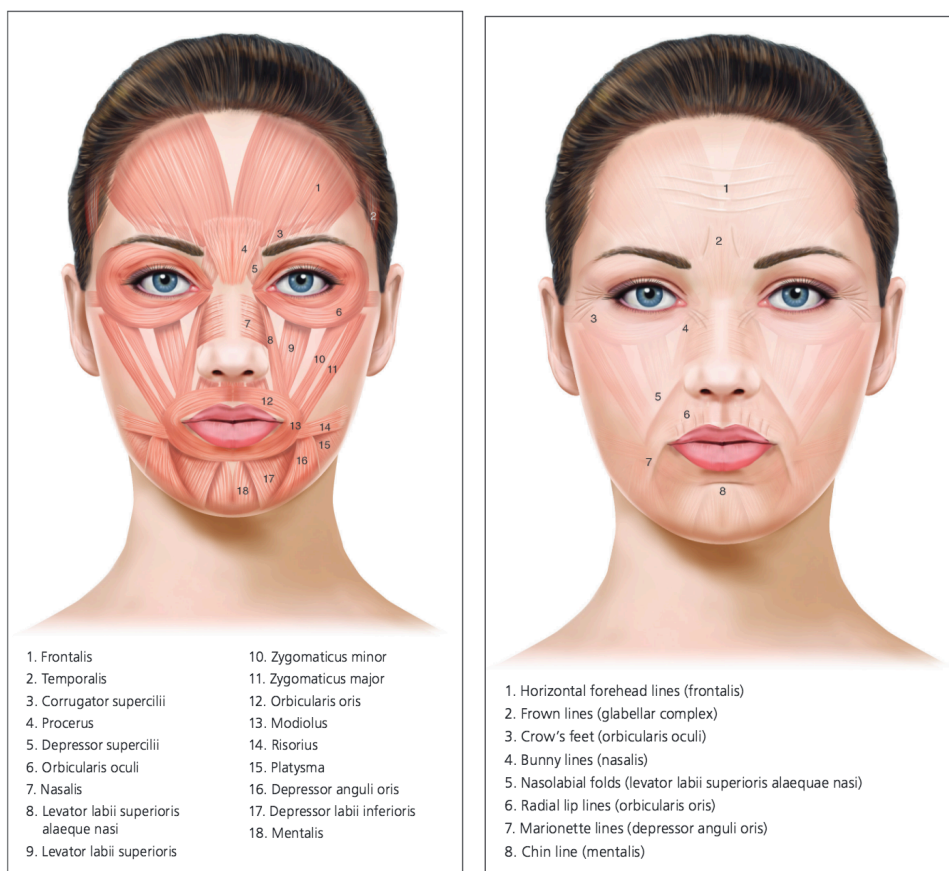
The disconnect between the social interpretation of one's facial expression and that person's actual emotion can lead to a miscommunication. For example, a patient with this problem might be asked "Why are you angry?" or "Are you tired today?" when the patient feels pleasant and rested. This inability to accurately communicate feelings and intentions becomes frustrating for the individual and puts them at a higher risk for anxiety and depression.<sup>9</sup> Many patient receive BTA injections not to increase their attractiveness, but to remove the lines that cause false negative expressions and prevent the social implications of facial expression miscommunication.<sup>10</sup>

The perceived age of one's face has a significant effect on the societal interpretation of its attractiveness. "Individuals perceived to be attractive receive preferential treatment in education, employment, medical care, legal proceedings, and

romantic encounters, that often result in their being happier, more successful, more socially adept, and more sexually fulfilled than others.”<sup>7</sup> Youthful appearance in females is a sign of beauty in many cultures as it represents health and fertility.<sup>7</sup> It also is associated with desirability, sexuality, and success, whereas aging can imply inadequacy and decrepitude.<sup>11,12</sup> Individuals that maintain a more youthful appearance as they age tend to be healthier and live longer with a positive outlook on life.<sup>13</sup> BTA injections eliminate wrinkles and returns patients to their more youthful appearance. Treatment with BTA is also used to increase facial symmetry, which is a standard of beauty across many cultures.<sup>7</sup>

An individual’s attractiveness has an effect on their self-esteem and how the individual is perceived by others. An attractive person is likely to receive positive responses, which promotes positive self-image and psychological health. The person’s perceived emotional state also impacts their social interactions. A smile or pleasant expression is more likely to elicit a smile from another person. This positive response results in continued positive behavior and enhanced interpersonal relationships. BTA injections allow individuals to look their best, which enhances their self-esteem and gives them a more optimistic attitude about social interactions. BTA injections also give the patient a more relaxed baseline expression that elicits a more positive response from others. The attractive, youthful, and pleasant appearance from BTA treatment results in improved psychological well-being and social functioning for that leads to a better quality of life for the patient.<sup>7</sup>

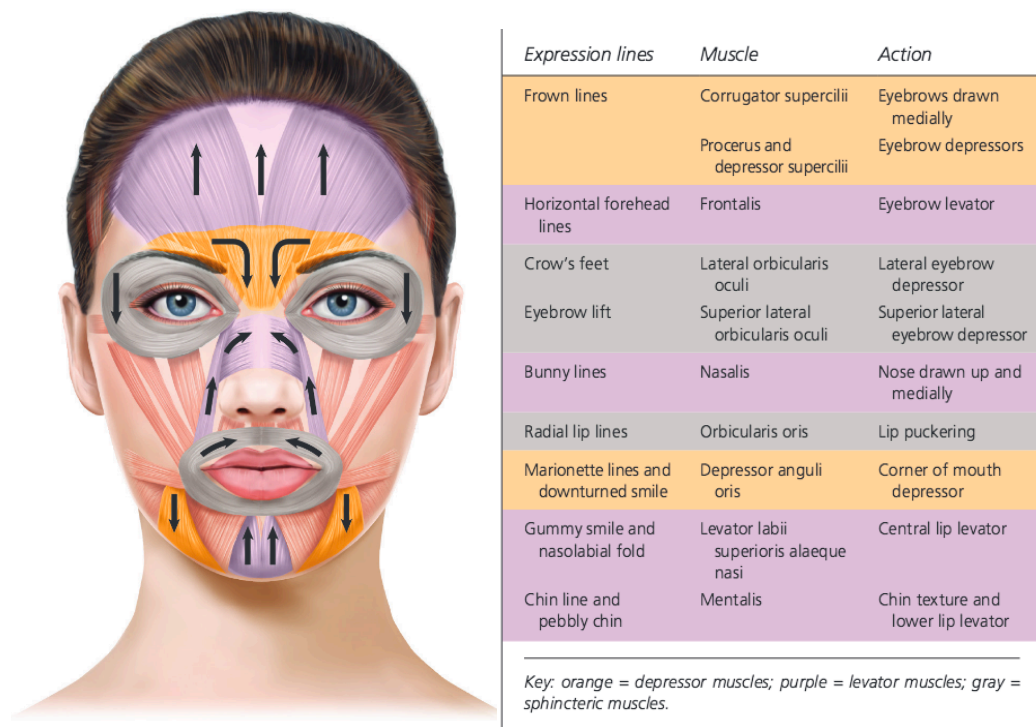
Wrinkles that cause facial aging are produced through a combination of repetitive muscle contraction and dermal atrophy. Rather than attaching to bone like most muscles, facial muscles have soft tissue attachments to skin through the superficial muscular aponeurotic system. Contracting these muscles causes the overlying skin to move and form dynamic wrinkles perpendicular to the direction of muscle contraction (Figure 2).<sup>14</sup>



**Figure 2. Musculature and wrinkles of the face<sup>14</sup>**

Glabellar wrinkles, also known as “frown lines” and “11’s” (due to their appearance), are vertical lines between the eyebrows formed by the glabellar complex

depressor muscles.<sup>14</sup> These muscles include the procerus, corrugator supercilii, and depressor supercilii and their contraction pulls the eyebrows inferiorly and medially.<sup>14</sup> Horizontal forehead lines are produced by the contraction of the frontalis muscle which moves the eyebrows superiorly.<sup>14</sup> Crow's feet are caused by contraction of the lateral orbicularis oculi moving the lateral eyebrow inferiorly (Figure 3).<sup>14</sup>



**Figure 3. Functional anatomy of the face.**<sup>14</sup>

All individuals will develop both dynamic and static facial wrinkles over the course of their lifetime. Dynamic wrinkles begin as early as childhood, while the onset of static wrinkles takes place in early to middle adulthood, depending on anatomy and skin quality. Facial wrinkle treatment includes microdermabrasions, chemical peels, laser

therapy, topical creams, topical retinoids, surgical correction, injectable dermal fillers, and botulinum toxin injections (Table 1). Avoidance of UV rays, application of sunscreen, and possibly the early injection of botulinum toxin can help delay the onset of static wrinkles.

**Table 1. Facial Wrinkle Treatment Options**

<b>Microdermabrasion</b>	Superficial skin resurfacing technique using aluminum oxide crystals to partially ablate the skin <sup>15</sup>
<b>Chemical peel</b>	Chemical agents (alpha or beta-hydroxy acids, Jessner's solution, trichloroacetic acid, and phenol-croton oil combination) are used to resurface skin at either superficial, medium, or deep level <sup>16</sup>
<b>Laser therapy</b>	Ablating the entire epidermis using CO2 or Er:YAG laser to resurface skin <sup>17</sup>
<b>Topical creams</b>	A variety of active ingredients (alpha-hydroxy acids, ascorbic acid, vitamin E, alpha lipoic acid, niacinamide, and N-acetyl-glucosamine) promote youthful skin <sup>18</sup>
<b>Topical retinoids</b>	Retinol (vitamin A) derivatives, most commonly tretinoin, efface wrinkles by forming a repair zone of new collagen in the papillary dermis <sup>19</sup>
<b>Botulinum toxin injections</b>	Decreases wrinkles by temporarily paralyzing the muscles that are responsible for their formation
<b>Injectable dermal fillers</b>	Hyaluronic acid or other substances injected into the face to provide volume where collagen has degraded over time <sup>20</sup>
<b>Surgical correction</b>	Plastic surgeons perform rhytidectomies (face lifts) and other procedures to eliminate wrinkles and signs of aging of the face <sup>21</sup>

BTA was first identified in 1895 and isolated in the 1920s.<sup>22</sup> Initially, BTA



treated only strabismus. However, it is now indicated for a variety of uses including cosmeses of facial lines, bladder dysfunction, chronic migraine, upper limb spasticity, cervical dystonia, primary axillary hyperhidrosis, and blepharospasm. Although its cosmetic use began in the 1980s, the first systematic study on its efficacy and safety was not published until 1992.<sup>22</sup> To date, BTA is well-researched. There are numerous double-blind, placebo-controlled studies showing BTA to have excellent efficacy and safety in the cosmetic treatment of glabellar, canthal, and chin rhytides.<sup>23</sup> Currently, BTA is approved by the U.S. Food and Drug Administration for the cosmetic treatment of frown lines by the glabellar complex (2002) and crow's feet by the orbicularis oculi muscles (2013).<sup>14</sup> While it is widely used for lines in the upper one-third of the face, it is also used off-label to treat the lower two-thirds.<sup>14</sup>

Botulinum toxin type A is one of eight serotypes of neurotoxin produced by the bacteria *Clostridium botulinum*.<sup>14</sup> The toxin inhibits the release of acetylcholine from peripheral cholinergic and ganglionic nerve terminals; this causes paralysis by disrupting the neurotransmission required for muscle contraction.<sup>24</sup> The molecular mechanism is well characterized. BTA cleaves synaptosomal-associated protein of 25 kDa (SNAP-25), a docking protein on the internal surface of neuronal membranes.<sup>24</sup> This prevents vesicle fusion and the release of acetylcholine.<sup>14</sup> SNAP-25 regenerates over time, allowing neuromuscular signaling and muscle contractility to eventually return.<sup>24</sup>

There are currently three BTA preparations; onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), and incobotulinumtoxinA (Xeomin®).<sup>14</sup> Complexing proteins surrounding the 150 kDa core botulinum neurotoxin vary depending on the

preparation.<sup>14</sup> The preparations are not interchangeable due to their differences in dosing, formula, and clinical response.<sup>14</sup>

Elective cosmetic treatment with botulinum toxin is not covered by insurance. The average units needed are 20 for the glabellar complex, 24 for forehead, and 12 per each set of crow's feet. Treatment of forehead and glabella lines requires 40 units on average. Each unit is priced between \$10-16, which amounts to \$400-640 per treatment. The cost is compounded by the toxin's half life. The paralysis effect of botulinum toxin lasts 3-6 months depending on the patient's metabolism of the drug.<sup>25</sup> Taken together, patients getting four treatments per year can spend up to \$2,560 annually.

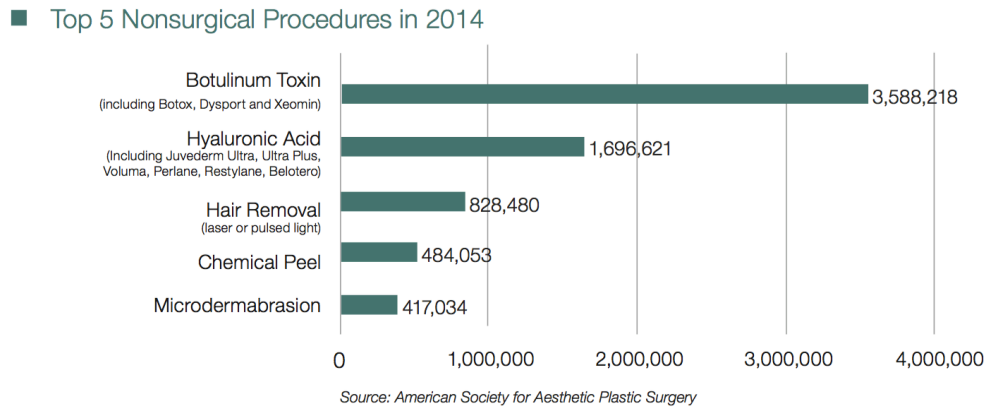
Since treatments are not covered by insurance, expense is the main limiting factor when it comes to starting age and frequency of BTA injections.<sup>5</sup> If patients wait too long and lines become imprinted, they would need to be treated with dermal fillers that are much more expensive per treatment than botulinum toxin.<sup>2</sup> However, if lines have appeared, but have not become permanent, then botulinum toxin would be effective in reducing or eliminating these lines. Thus, botulinum toxin can be initiated as prevention or as treatment following initial appearance. To date, however, there are no studies showing the optimal time to initiate treatment from a cost-effectiveness standpoint.

The prophylactic use of botulinum toxin to prevent facial line development and imprinting is demonstrated by a twin study published in JAMA Facial Plastic Surgery in 2006.<sup>2</sup> The first twin received botulinum toxin injections to the forehead and glabella 2-3 times per year for 13 years while the second twin received just two treatments in her 30s. Results showed that "imprinted forehead and glabellar lines were not evident in the

regularly treated twin, but were evident in the minimally treated twin.”<sup>2</sup> The authors concluded that “long-term treatment with botulinum toxin can prevent the development of imprinted facial lines that are visible at rest.”<sup>2</sup> However, this study does not address the initiation of regular treatment soon after lines begin to form. It is not known what the results would be if the minimally treated twin began regular botulinum toxin injections in her 30s instead of her two sporadic treatments.

There are many documented benefits to botulinum toxin prophylaxis prior to the development of facial lines. Cost per treatment is significantly less with prophylaxis than for treatment once lines develop. Additionally, some patients experience a longer period of effectiveness after consistent treatments.<sup>5</sup> This further contributes to cost reduction. Patients with consistent treatments also benefit behaviorally. Patients with constant paralysis of facial muscles eventually learn to stop trying to contract these muscles for everyday facial expressions.<sup>25</sup> The literature suggests this further prevents line development and may facilitate dermal remodeling.<sup>25</sup> Lastly, there is no imprinting of lines thus there is no need for more expensive treatments with dermal fillers in the future. Disadvantages of therapy include long-term out of pocket expenses, early initiation of treatment (in the patient’s 20s), as well as the inconvenience of many years of regular office visits.

The use of BTA to treat the facial wrinkles associated with aging is steadily increasing. According to the American Society for Aesthetic Plastic Surgery, BTA treatment has been the most popular nonsurgical procedure since 2000.<sup>3</sup> In 2014 alone, clinicians performed just under 3.6 million procedures. (Figure 4).



**Figure 4: Top 5 Nonsurgical Procedures in 2014<sup>3</sup>**

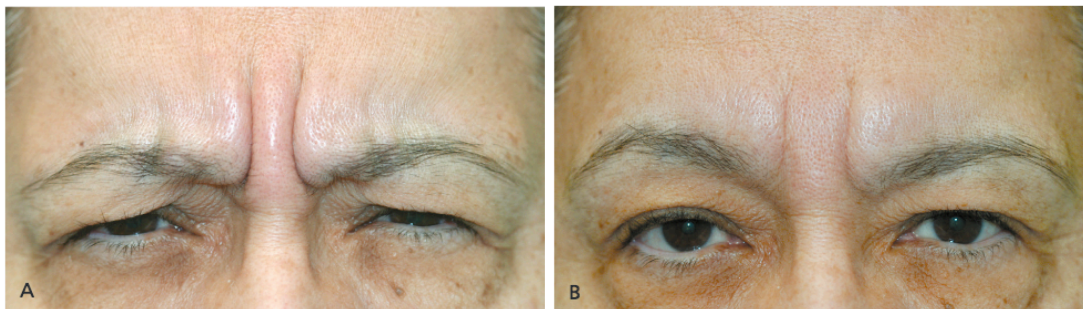
BTA is administered as an intramuscular injection to facial muscles implicated in the development of wrinkles. An aesthetic consultation is first performed to determine the patient's areas of concern and to discuss treatment options, expected results, and complications. The patient's face is evaluated for asymmetries, such as uneven eyebrow height or eye aperture. Both dynamic and static photographs are taken before treatment to serve as comparisons for future visits.

Setting realistic expectations for the results of treatment outcome is important during the consultation as therapeutic response varies. Patients with only dynamic wrinkles typically demonstrate significant improvement with the first treatment (Figure 5).<sup>14</sup> These patients are using BTA prophylactically to prevent static line development. Patients with static lines at rest may require two to three consecutive treatments before any noticeable results (Figure 6).<sup>14</sup> Deep static lines that have become imprinted are often refractory to BTA alone and require additional treatments, such as dermal fillers, in order to achieve desired results. Manually stretching the skin perpendicular to static lines can

indicate if they are imprinted. If the lines disappear with stretching, they are not imprinted and they will likely respond to BTA injections. The reverse also holds true; imprinted wrinkles could be refractory to BTA treatment and may require a dermal filler for cosmetic improvements.



**Figure 5. “Ideal candidate for botulinum toxin treatment demonstrating (A) dynamic frown lines with glabellar complex muscle contraction and (B) lack of static lines with glabellar muscles at rest.”<sup>14</sup> Copyright © Rebecca Small, MD.**



**Figure 6. “(A) Dynamic frown lines with glabellar complex muscle contraction and (B) static lines with glabellar muscles at rest.”<sup>14</sup> Copyright © Rebecca Small, MD.**

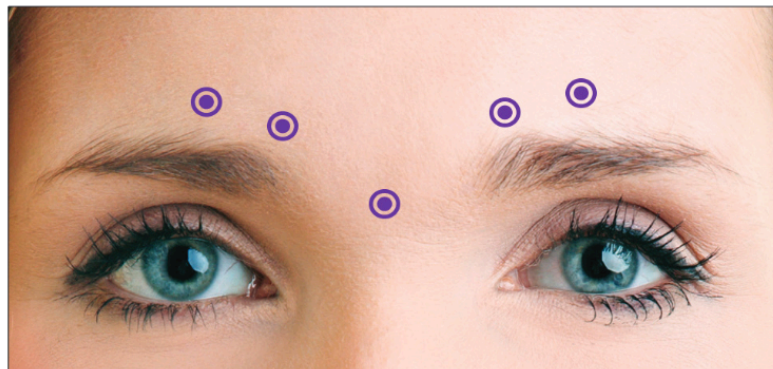
There are several contraindications to cosmetic treatment with BTA injections. Physiologic contraindications include allergies to BTA product contents, neuromuscular disorders, and keloidal scarring. Relative social and psychiatric contraindications include unrealistic expectations, profession involving the use of facial expressions, and body dysmorphic disorder (Table 2).<sup>14</sup>

**Table 2. Contraindications to Botulinum Toxin Injection<sup>14</sup>**

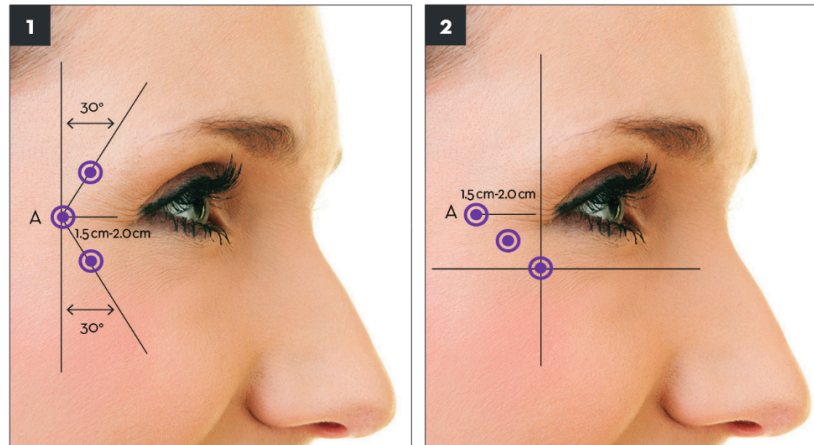
<b>Contraindications</b>
<b>Sensitivity or allergy to constituents of the botulinum toxin product (e.g., cow's milk protein allergy with abobotulinumtoxinA)</b>
<b>Neuromuscular disorder (e.g., amyotrophic lateral sclerosis, myasthenia gravis, Lambert-Eaton syndrome, myopathies)</b>
<b>Gross motor weakness in the treatment area (e.g., Bell palsy)</b>
<b>Dermatoses in the treatment area (e.g., psoriasis, eczema)</b>
<b>Infection in the treatment area</b>
<b>Pregnancy or breastfeeding</b>
<b>Immunocompromised</b>
<b>Keloidal scarring</b>
<b>Body dysmorphic disorder</b>
<b>Unrealistic expectations</b>
<b>Dependency on facial expression for livelihood (e.g., actors, singers)</b>

BTA injections are performed on an outpatient basis and do not require anesthesia. Clinicians instruct patients to hold an ice pack on the injection site during BTA product preparation. After the skin is sterilized, the patient is asked to contract muscles (“frown,” “raise eyebrows,” “smile,” etc.) to show dynamic wrinkles and provide the clinician with better visualization of targeted injection sites. The clinician

then injects up to 1ml of solution using a 30-gauge, 1-inch needle.<sup>14</sup> The glabellar complex is treated with injections into five sites: the midline of the procerus and bilaterally in the medial and midlateral corrugators (Figure 7).<sup>26</sup> Crow's feet are treated with three injection sites in the orbicularis oculi based on wrinkle location relative to the lateral canthus of the eye (Figure 8).<sup>26</sup> Horizontal forehead lines are often treated by a series of injections 1-2cm apart across the medial forehead. After the injections are completed, patients are instructed to avoid certain activities to prevent unwanted spread of the toxin. Patients should avoid lying supine for four hours, massaging or heating the area, exercise, alcohol, and using hot tubs on the day of treatment.<sup>14</sup>



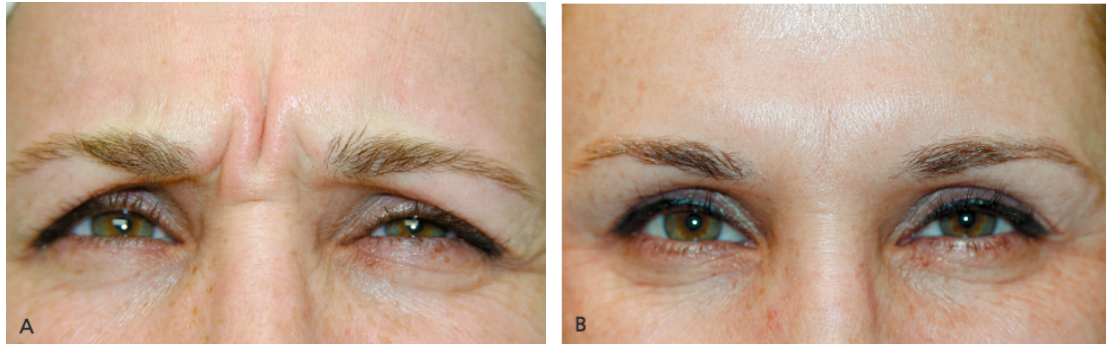
**Figure 7. Glabellar complex injection sites.**<sup>26</sup>



**Figure 8. Crow's feet injection sites. 1) If lines are above and below the lateral canthus. 2) If lines are primarily below the lateral canthus.<sup>26</sup>**

The effects of BTA injections can be seen as early as 3 days following treatment, while maximal results are seen around two weeks (Figure 9).<sup>14</sup> Generally, the effects last three to four months, but they gradually diminish over that period. After multiple treatments, therapeutic effects may last longer for some patients, allowing extension of treatment intervals.





**Figure 9. Dynamic frown lines with glabellar complex muscle contraction (A) before and (B) one month after onabotulinumtoxinA (Botox) treatment.**<sup>14</sup> Copyright © Rebecca Small, MD.

There are a few complications associated with BTA injections. Burning or stinging at the injection site during the procedure is common and resolves within a few minutes. Additional complications are more rare, but include injection reactions and undesired BTA effects (Table 3).<sup>14</sup> Injection reactions such as erythema, edema, tenderness, and headache usually resolve within a few days. Bruising can take up to a few weeks to resolve, but may be treated with ice or pressure to prevent worsening.

Undesired effects of BTA are rare, but more distressing for patients. Most are due to BTA migration outside the treatment area. Migration causes paralysis of adjacent muscles not implicated in wrinkle formation. The incidence of these undesired effects declines with provider experience. Asymmetry and eyebrow ptosis can be caused by uneven dosing of BTA. Blepharoptosis, or upper eyelid droop, is due to “deep migration of botulinum toxin through the orbital septum fascia to the levator palpebrae superioris, an upper eyelid levator muscle” and can be prevented by keeping corrugator injections

1cm superior to the supraorbital ridge at the midpupillary line (Figure 10).<sup>14</sup>

**Table 3. Complications with Botulinum Toxin Injection<sup>14</sup>**

Injection Reactions	Undesired Botulinum Toxin Effects
Anxiety or vasovagal episode	Allergic reaction
Ecchymosis	Antibodies against BTA
Erythema, edema, and tenderness	Blepharoptosis
Headache	Distant spread from injection site
Infection	Eyebrow ptosis
Pain	Facial asymmetry
Paresthesia or dythesia	Medication interactions
	Undesired eyebrow shape



**Figure 10. “Right-sided blepharoptosis three weeks after botulinum toxin treatment of the glabellar complex for frown lines.”<sup>14</sup> Copyright © Rebecca Small, MD.**

## **Existing research**

The first study documenting the use of BTA injections for treatment of glabellar lines was published in 1992.<sup>27</sup> While it demonstrated the efficacy and safety of treatment with BTA, the study only included 17 subjects and lacked a control group.<sup>27</sup> Likewise, double-blind, placebo-controlled studies in 1994 and 1996 showed significant safety and efficacy of BTA treatment, but included only 41 patients total.<sup>28,29</sup>

Carruthers et al (2002) was the first large scale double-blind, placebo-controlled, randomized, multi-center, clinical trial on the efficacy and safety of BTA injections for the treatment of glabellar lines.<sup>5</sup> Two-hundred and sixty-four patients (203 BTA, 61 placebo) received 20 unit injections to the glabellar complex muscles and followed-up at 7, 30, 60, 90, and 120 days after the procedure. The study assessed physician-graded glabellar line severity, patient assessment of improvement, and adverse events.<sup>5</sup>

Results of this study demonstrated significant improvement of glabellar lines when compared to placebo. Physicians graded lines (0 = none, 1 = mild, 2 = moderate, 3 = severe) at baseline before treatment. At follow-up days 7, 30, and 60 the BTA group showed a mean improvement of 1.5 grades. At day 90 and 120, mean improvement in BTA group was 1.0 and 0.5 grades, respectively. Placebo group showed no improvement from baseline on any follow-up day. Patients used a 9-point scale (+4 = 100%, 0 = no improvement, -4 = 100% worse, each point = 25% change) to rate the improvement of their glabellar lines. The mean improvement scores of the BTA group were +3.0 at 30 days, +2.7 at 60 days, +2.1 at 90 days, and +1.4 at 120 days. Mean improvement in the placebo group remained near zero at all follow-ups.<sup>5</sup>

The adverse events observed were headache in 15% of patients in both groups and blepharoptosis in 5.4% BTA patients versus 0% in the placebo group. Most cases of headache and blepharoptosis were mild demonstrating that BTA is an overall safe procedure.<sup>5</sup>

The 2002 study was repeated in 2003 with the same measures and confirmed the results.<sup>25</sup> In the follow-up study, 273 patients enrolled (202 BTA, 71 placebo). Physician-rated mean improvement score for the BTA group was approximately 1.0 on days 7, 30, and 60, 0.75 on day 90, and 0.5 on day 120. The placebo group showed no improvement at any date. Patient-rated improvement in the BTA group was +3.0 at 30 days, +2.6 at 60 days, +1.9 at 90 days, and +1.0 at 120 days. The placebo group showed little to no improvement at all follow-ups. Adverse events were also similar. Headache was reported in 11% of BTA patients and 20% placebo. Blepharoptosis was present in 1% of the BTA group and 0% of the placebo group.<sup>25</sup>

Now that the efficacy of BTA injections had been confirmed, Heckmann et al (2003) went a step further and showed the treatment's impact on baseline expressions of the face.<sup>10</sup> Forty volunteers first rated 102 incremental variations of 3 male and 3 female prototype faces. These faces were morphed by a computer program to display 0%, 25%, 50%, 75%, and 100% of happiness, sadness, fear, or anger. One volunteer was unable to make this differentiation and was excluded from the data analysis. The others went on to rate the images of 20 patients before and 1 week after BTA injections.

Results indicated that BTA injections enhanced the patients baseline expression of happiness and decreased baseline expression of the other negative emotions. Happiness

was the least expressed emotion before treatment, but increased by 71% to become the most expressed emotion after treatment. Expression of sadness only decreased by 10%, but fear and anger decreased significantly, 49% and 40% respectively.<sup>10</sup> These results indicate that BTA injections give patients a more pleasant expression at baseline, which will lead to more positive social interactions and eliminate the emotion-expression mismatch observed with facial aging.<sup>7</sup>

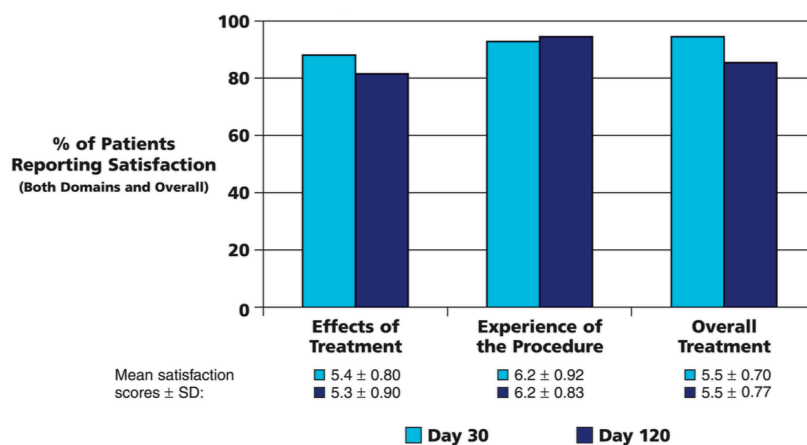
It is well-documented that patient satisfaction with BTA treatment is high, but methods of assessing satisfaction have been inconsistent between studies.<sup>30,31</sup> Sommer et al (2003) used a general cosmetic dermatology assessment, not specifically for facial rhytides, while Foster et al (2007) used a non-standardized questionnaire. These studies achieved overall satisfaction rates of 80% and 90%, respectively.<sup>30,31</sup>

The development of the Facial Lines Treatment Satisfaction Questionnaire provided a standardized, validated, and reliable method of assessing patient satisfaction with BTA injections.<sup>32</sup> Stotland et al (2007) used the Facial Lines Treatment Satisfaction Questionnaire to measure satisfaction regarding the results and procedure after BTA injections.<sup>4</sup> In this study, 56 women with moderate to severe glabellar rhytides received 20 units of BTA in the corrugator and procerus muscles, and were evaluated 30 days and 120 days after treatment. Patients were assessed in the following areas: investigator- and patient-rated global assessment of change in severity, patient self-perception of age, and patient satisfaction of the procedure and effects of treatment using the Facial Lines Treatment Satisfaction Questionnaire (Table 5 below).<sup>4</sup>

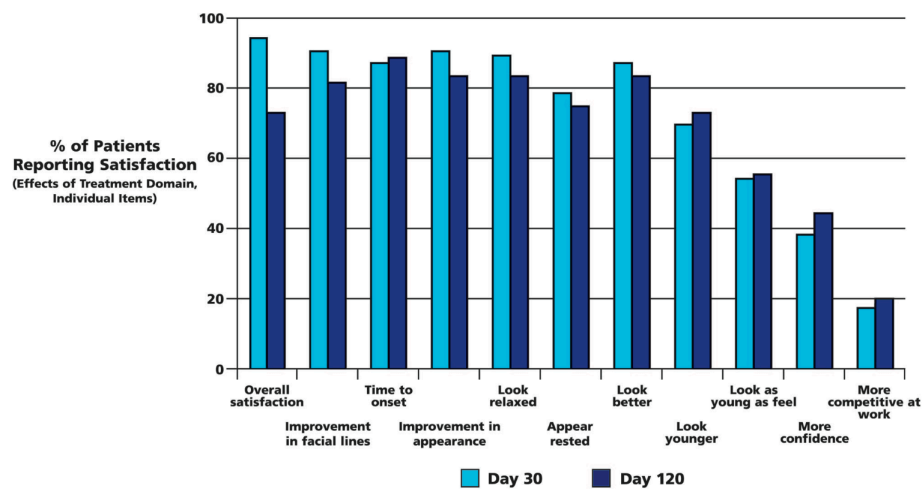
The results showed physicians and patients both reported significant improvement

in glabellar line severity at day 30 and day 120.<sup>4</sup> Thirty-seven percent of patients perceived to look younger after treatment at day 30, while 34% believed so at day 120. Patients perceived that they looked a median of 5 years younger. None of the patients thought they looked older after receiving the BTA injections.<sup>4</sup>

Patient satisfaction was high. The overall satisfaction rates were 95% at day 30 and 86% at day 120, and there was a mean total score of greater than or equal to five on the Facial Lines Treatment Satisfaction Questionnaire (Figure 11).<sup>4</sup> Eighty-eight percent of patients at day 30 and 82% at day 120 reported satisfaction (i.e., greater than or equal to a score of 5) in the effects of treatment domain. Ninety-three percent of patients at day 30 and 95% at day 120 reported satisfaction in the procedure experience domain. The majority of patients also reported satisfaction in the individual items in both domains of the Facial Lines Treatment Satisfaction Questionnaire (Figure 12).<sup>4</sup>



**Figure 11. Percent satisfaction in each domain and overall treatment of the Facial Lines Treatment Satisfaction Questionnaire<sup>4</sup>**



**Figure 12. Percent satisfaction in the Effects of Treatment Domain of the Facial Lines Treatment Satisfaction Questionnaire<sup>4</sup>**

The use of the Facial Lines Treatment Satisfaction Questionnaire proved to be effective in assessing patient satisfaction with the BTA procedure and outcomes, but there were limitations to this study. The individual items on the questionnaire were not assessed at baseline before the procedure. Additionally, there is a major conflict of interest present in this study as Allergan Inc. provided the funding. This pharmaceutical company produces Botox, the most widely used brand of BTA.

There are no current studies demonstrating an association between age and effects of treatment with BTA. Many hypothesize that injections prior to the development of facial lines will prevent wrinkle formation by inhibiting repeated contraction of muscles implicated in their development. This theory makes sense from a biomechanics and physiologic standpoint, but there are downsides in practice. Most notably, earlier treatment equates to increased costs. Conversely, there is also the chance that upfront

spending on prophylactic treatment will result in reduced long-term costs, as more extreme forms of treatment will not be necessary.

The only study comparing age and treatment outcomes with BTA is a twin study published in JAMA Facial Plastic Surgery in 2006. The first twin received botulinum toxin injections to the forehead and glabella 2-3 times per year for 13 years. The second twin received only 2 treatments, one at age 31 and one at age 35. Photographs were taken of both twins (age 38) 4 months after the regularly treated twin's last treatment. Results showed that "imprinted forehead and glabellar lines were not evident in the regularly treated twin, but were evident in the minimally treated twin"<sup>2</sup> (Figure 13). The authors concluded, "long-term treatment with botulinum toxin can prevent the development of imprinted facial lines that are visible at rest."<sup>2</sup>





**Figure 13. The minimally treated twin (A, B, and C) and the regularly treated twin (D, E, and F). Hyperfunctional lines in the forehead (B and E) and glabellar regions (C and F) are visible in the minimally treated twin but not in the regularly treated twin.<sup>2</sup>**

Although the results appear to show a dramatic difference between the twins, this study has many limitations. First, it does not address prophylactic treatment versus the initiation of regular treatment soon after lines begin to form. Second, this study is funded by Allergan, the maker of Botox – this is a significant conflict of interest and reasonably questions the objectivity of the study. Third, the study is limited by its small sample size as results are not applicable to larger populations.

## **METHODS**

### **Study design**

The study design will be a retrospective study to determine if there is a correlation between starting age of BTA injections and patient satisfaction rates.

### **Study population and sampling**

The study population will include dermatology patients from Boston Medical Center (BMC). Patients eligible for the study are females between the ages of 40 and 50 who received BTA injections for cosmetic treatment of facial wrinkles. Patients will be recruited by telephone and will be asked to complete the Facial Lines Treatment Satisfaction Questionnaire. If the patient completes the survey and does not meet exclusion criteria (Table 4), they will be included and their chart will be reviewed for age at initial treatment with BTA.

A sample size of 500 patients, 250 patients per group, will be used in order to obtain a 10% difference in satisfaction rating between groups with a power of 0.80, type I error rate of 5%, and sampling ratio of 0.75.<sup>33</sup>

**Table 4. Exclusion criteria<sup>4</sup>**

Received BTA injections at location other than BMC
Received other facial rejuvenation treatments
Undergone facial aesthetic surgery
Had a significant facial movement disorder
Preexisting brow or eyelid ptosis
History of CVA, head injury, or other cerebral damage affecting the recognition or expression of emotion
Had any psychiatric illness that might interfere with the ability to produce facial expressions or experience emotion normally
Had any disorder or were using any agent that might interfere with neuromuscular function
Keloidal scarring

### **Study variables and measures**

The patients will be asked to rate their satisfaction using the validated Facial Lines Treatment Satisfaction Questionnaire (Table 5), in which patients rate their satisfaction on a seven-point scale (where 1 = very dissatisfied, 2 = dissatisfied, 3 = somewhat dissatisfied, 4 = neutral, 5 = somewhat satisfied, 6 = satisfied, and 7 = very satisfied).<sup>4</sup>

The mean score of all of the items will be calculated. Patients with a mean score of at least 5 will be considered to have achieved satisfaction.<sup>4</sup>

**Table 5. Facial Lines Treatment Satisfaction Questionnaire<sup>32</sup>**

“Please rate your satisfaction in these areas.”	Very dissatisfied	Dissatisfied	Somewhat dissatisfied	Neutral	Somewhat satisfied	Satisfied	Very Satisfied
<b>Overall satisfaction</b>	1	2	3	4	5	6	7
<b>Improvement of facial lines</b>	1	2	3	4	5	6	7
<b>Time to onset</b>	1	2	3	4	5	6	7
<b>Improvement in appearance</b>	1	2	3	4	5	6	7
<b>Look relaxed</b>	1	2	3	4	5	6	7
<b>Appear rested</b>	1	2	3	4	5	6	7
<b>Look better</b>	1	2	3	4	5	6	7
<b>Look younger</b>	1	2	3	4	5	6	7
<b>Look like you feel</b>	1	2	3	4	5	6	7
<b>Confidence</b>	1	2	3	4	5	6	7
<b>Competitive at work</b>	1	2	3	4	5	6	7

Patients that complete the Facial Lines Treatment Satisfaction Questionnaire will undergo a chart review to determine the age at which they began receiving BTA injections. Patients will then be split into two groups for further analysis. Patients who began BTA injections before age 35 will be compared to those who began injections at age 35 or older.

### **Recruitment**

All female patients ages 40-50 who have received BTA injections as a cosmetic treatment at BMC will be recruited by telephone and asked to answer the eleven items on the effects of treatment domain of the Facial Lines Treatment Satisfaction Questionnaire. All patients fitting the criteria will be contacted to ensure enough agree to answer the questionnaire to obtain a sample size of at least 500.

**Data collection**

The investigator will obtain the electronic medical record of all patients in the sample population. The investigator will locate the contact information in the chart and call the patient. The investigator will conduct the telephone interview of the patient and record the responses. The investigator will then locate the record of the patient's first BTA treatment and record the patient's age at this time.

**Data analysis**

Data will be analyzed with a McNemar's chi square test and logistic regression will be performed to measure strength of the associated odd's ratio. Due to confounding variables such as age, frequency of treatment, and number of areas treated, cases and controls will be matched by age  $\pm 2$  years, then matched logistic regression will be performed.

**Timeline and resources**

The study will be conducted over the course of one year. The resources necessary include investigators to conduct the Facial Lines Treatment Satisfaction Questionnaire and at least one statistician to analyze the data collected. Overall this study is cost-effective with labor being the greatest expense.

**Institutional Review Board**

The study will be submitted for review to the Boston University Medical Campus IRB for expedited review. Expedited review is appropriate as this study is a phone questionnaire

and there is no clinical intervention being performed. This study is low-risk and patient confidentiality will be protected. Only investigators will have access to patient information. Patient identifiers will be removed before data is analyzed and published.

Budget line items: Administrative Support

- Clerical (Wages)
- Data entry
- Statistical consulting

## **CONCLUSION**

### **Discussion**

The results of the study will determine if there is a correlation between younger starting age of BTA treatment and higher satisfaction rates. Satisfaction in this sub-group has not yet been studied and the sample size proposed is significantly larger than all of the previous research on BTA treatment satisfaction. This study is relatively cost effective (labor is the main expense) and it can be reproduced by any institution that offers cosmetic BTA treatment.

This study is limited due to the subjective nature of the data from the Facial Lines Treatment Satisfaction Questionnaire. The selection bias from the voluntary questionnaire will affect the data that is collected. The results are not likely to be generalizable because patients from only one medical center were included.

Even if patients that begin BTA injections before 35 are more satisfied, it does not necessarily indicated that the long term treatment is more efficacious. A prospective clinical trial with objective data measures is needed to confirm if earlier initiation of BTA injections is superior. Higher satisfaction scores on the Facial Lines Treatment Satisfaction Questionnaire among patients who started treatments before 35 would justify this prospective study as patients with better results are more likely to be satisfied.

### **Summary**

BTA injections are the most popular cosmetic treatment for the facial wrinkles associated with aging. Many patients are beginning treatments in their 20s before static facial lines develop as a means of prophylactic treatment and wrinkle prevention even though there is



no significant data supporting this concept. If this study demonstrates higher satisfaction rates in patients who begin BTA injections before age 35, then there is likely an association between early starting age and development of fewer facial wrinkles.

All research on BTA treatment satisfaction demonstrated high satisfaction rates with the procedure and results. One of these studies even noted that results were superior on younger patients verses older patients, but research on starting age has not been conducted.<sup>5</sup> The validated and reliable Facial Lines Treatment Satisfaction Questionnaire given to a large sample size of patients stratified by age would be a cost-effective method to provide evidence for allocating resources to future clinical trials.

### **Clinical Significance**

As the average lifespan increases, patients no longer feel as old as they look and many are turning to cosmetic treatments such as BTA injections in order to bridge the aesthetic gap. Many patients are frustrated by facial aging changing their baseline expression to reflect an angrier, irritated, and tired appearance. An early start to BTA injections would prevent these facial changes keeping the patient's baseline expression more pleasant. This leads to more positive social interacts for the patient. These enhanced interpersonal relationships as well as increased youthful attractiveness elevate the patient's self-esteem. Although some oppose this procedure as it is for a cosmetic, not medical, indication, the confidence and improved communication gained as a result of early-initiated BTA injections significantly enrich quality of life for the patient.

BTA is the most popular nonsurgical cosmetic procedure, but there is no data demonstrating an ideal age to begin treatment. Results of this study would provide merit

further research that would indicate the starting age that provides the patient with optimal treatment outcomes. Patients would then be able to obtain the most cost-effect treatment plan while avoiding the social and psychological consequences of the aging face.

## LIST OF JOURNAL ABBREVIATIONS

Aesthetic Plast Surg	Aesthetic Plastic Surgery
Aesthet Surg J	Aesthetic Surgery Journal
Ann Plast Surg	Annals of Plastic Surgery
Arch Facial Plast Surg	Archives of Facial Plastic Surgery
Clin Dermatol	Clinicis in Dermatology
Clin Interv Aging	Clinical Interventions in Aging
Dermatol Surg	Dermatologic Surgery
Dis Mon	Disease-a-Month
J Am Acad Dermatol	Journal of the American Academy of Dermatology
J Cosmet Dermatol	Journal of Cosmetic Dermatology
J Dermatol Surg Oncol	Journal of Dermatologic Surgery and Oncology
J Drugs Dermatol	Journal of Drugs in Dermatology
JAMA Dermatol	JAMA Dermatology
Lasers Surg Med	Lasers in Surgery and Medicine
Otolaryngol Head Neck Surg	Otolaryngology – Head and Neck Surgery
Pharmacother J Hum Pharmacol Drug Ther	Pharmacotherapy: The Journal of Pharmacology and Drug Therapy
Plast Reconstr Surg	Plastic and Reconstructive Surgery
Psychol Sci	Psychological Science

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## CURRICULUM VITAE

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### Licenses and Certifications

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- Volunteer Instructor, Ride for the Muscular Dystrophy Society, March 2016
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