A Randomized, Single-Blind, Crossover Study Evaluating the Impact of OnabotulinumtoxinA Treatment on Mood and Appearance During the COVID-19 Pandemic

Robert T. Cristel, MD; Nimit D. Gandhi, MD; Tariq Z. Issa, BA; Eljona Kola, MS; Daniel Demesh, MD; and Steven H. Dayan, MD, FACS

Dr Cristel is a resident, Dr Demesh is a fellow, and Dr Dayan is an attending physician, Department of Otolaryngology, Head, and Neck Surgery, Division of Facial Plastic and Reconstructive Surgery, University of Illinois at Chicago, Chicago, IL. Mr Issa is a medical student, Feinberg School of Medicine, Northwestern University, Chicago, IL. Drs Gandhi and Kola, DeNova Research, Chicago, IL.

Corresponding Author: Dr Steven H. Dayan, DeNova Research, 845 N. Michigan Ave, Ste. 923 E, Chicago, IL 60611, USA.
E-mail: sdayan@drdayan.com; Instagram: @drstevendayan

Disclosures: Dr Dayan received a grant from Allergan plc to support the research for this article. The other authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding: This research was supported by a grant from Allergan plc for equipment, materials, and medications for this study.

Level of Evidence: 2 (Therapeutic)

Abstract

Background: The emergence of Coronavirus disease of 2019 (COVID-19), quickly became one of the most severe disease outbreaks in modern history. This caused many aesthetic practices around the country to close temporarily and led to a unique time period to evaluate the impact neurotoxin has in the setting of an ongoing pandemic.

Objectives: To examine whether the administration of onabotulinumtoxinA (BOTOX Cosmetic, Allergan plc, Coolock, Ireland), in regular users, synergistically amplifies the elevation in mood/happiness, self-satisfaction with appearance and overall satisfaction, in the context of the ongoing pandemic.

Methods: A randomized single-blind cross-over study was designed to evaluate the impact of neurotoxin treatment in the upper third of the face on mood, self-satisfaction with appearance, and overall satisfaction. The placebo group crossed over to treatment after 1 month. Surveys evaluating patient happiness, self-satisfaction with appearance and overall efficacy were completed among both groups, and again to the placebo group again following crossover to treatment.

Results: Forty-five subjects were enrolled with 30 in the treatment and 15 in the control/cross-over group. The placebo group demonstrated no change in happiness or self-satisfaction in appearance until cross-over to the treatment group. Both groups, once receiving, onabotulinumtoxinA reported increased happiness, self-satisfaction with appearance and overall treatment satisfaction.

Conclusions: OnabotulinumtoxinA treatment to the upper face in the midst of the COVID-19 pandemic was found to increase patient happiness, self-satisfaction with appearance, and overall treatment satisfaction.

The emergence of Coronavirus disease of 2019 (COVID-19), quickly became one of the most severe disease outbreaks in modern history[1]. As the contagion spread out of control, hospitals in major disease hotspots began to experience shortages in staffing, personal protective equipment, and other hospital resources. On March 13, 2020, the American College of Surgeons (ACS) became the first group to officially recommend to reduce and cancel elective procedures to mitigate the strain on the healthcare system[2]. Aesthetic procedure providers including plastic surgeons, facial plastic surgeons, and dermatologists all put their practices on hold in efforts to help conserve limited personal protective equipment (PPE) and limit unnecessary staff and patient exposures to the new contagion. In one survey of American Council of Academic Plastic Surgeons (ACAPS) providers, less than 10% of those offering aesthetic procedures prior to the pandemic were still offering those procedures in April[3].

At the same time, the pandemic forced non-essential workers to transition to a virtual life, with many employers shifting to video calls centering primarily one's face onto a screen for all their colleagues. Similarly, mask-wearing showcases the upper region of one's face while hiding the bottom two-thirds. Facial rhytides in the upper facial region are often associated both with signs of aging as well as signs of stress, anxiety and anger[4]. Potentially due to these effects, Google trends analysis showed growing interest in aesthetic procedures, especially facial plastic surgery procedures, as stay-at-home orders were initially being lifted[5,6]. Key trends in searches for neurotoxin treatments especially noted a decrease in decline over the first few months of the pandemic before rising to pre-pandemic levels immediately after stay-at-home orders were lifted.
The effects of the pandemic on non-naïve patient mood/happiness, self-satisfaction of appearance, and overall treatment satisfaction after neurotoxin treatment in the upper facial region has yet to be examined. Amidst the constraints of a global pandemic, many patients have exceeded their normal treatment interval and their glabellar wrinkles returned to baseline. This is a once in a lifetime period of time in which regular users of neurotoxin are not able to receive their regular injections. It would not be surprising that these patients are experiencing a decrease in their mood secondary to weeks of social isolating and distancing.

This unique time period allows the opportunity to evaluate the impact neurotoxin has on mood/happiness, self-satisfaction of appearance, and overall treatment satisfaction on non-naïve patients in the setting of the COVID-19 pandemic. We primarily aim to examine whether the administration of onabotulinumtoxinA (BOTOX Cosmetic, Allergan plc, Coolock, Ireland), in regular users, synergistically amplifies the elevation in mood/happiness beyond what would be achieved

had they not had treatment, in the context of the ongoing pandemic. We postulate that regular neurotoxin users have a secondary gain beyond wrinkle reduction, but also as a mood elevator.

We secondarily aim to examine the change in patient satisfaction and patient-reported efficacy in subjects returning for onabotulinumtoxinA treatment. Moreover, we aim to examine these effects against a placebo treatment to ensure that the changes in patient satisfaction are due to the neurotoxin treatment itself rather than other variables associated with their visit, such as easing of local and national restrictions due to COVID-19. We hypothesize high patient satisfaction and efficacy.

METHODS

A total of 45 subjects were included with 30 in the treatment arm and 15 in the control arm. The study date range was from 7/20/2020 to 09/03/2020. Eligible subjects were enrolled in a cohort that included men and women between the ages of 18-75 who were non-naïve neurotoxin users that were at least 20 weeks from their most recent neurotoxin treatment. Subjects were excluded if they had received neuromodulator injections in the glabellar region within 20 weeks prior to enrollment and did not have a 2-3 glabellar wrinkle severity score on the Allergan Facial Wrinkle Scale (FWS). Exclusion criteria included diagnoses of severe depression or bipolar disorder, recent changes in anti-depressant or anti-anxiety medications, known allergy or sensitivity to study ingredients. Females who were pregnant, attempting to get pregnant, or breastfeeding were also excluded from this study. To complete enrollment, all subjects were expected to understand the aspects of this study, provide their consent, and complete the required treatment and follow up visits. All study protocols were approved Advarra Institutional Review Board (Columbia, MD, USA).

Participation in the study occurred over the course of 3-4 visits and all procedures were performed by the senior author (S. H. D.). At the first visit, subjects were evaluated to meet inclusionary criteria and then randomized to either a treatment or control group. All subjects underwent standardized 2D photography and video at baseline. Subjects were photographed at rest and with maximal contraction (ie, while frowning) (Figure 1). Video was taken of the subjects while frowning, smiling, puckering, and reading of a short rhyme. All subjects in both groups completed two questionnaires at baseline: FACE-Q Appraisal of Lines Between Eyebrows[7] and Subject Happiness Scale (SHS)[8]. These were printed out and completed before any treatment or any contact with the study senior author (SHD) to prevent any potential bias. The study coordinator distributed the survey. The subjects were randomized with 30 in the treatment group and 15 in the control group. An online randomizer

at https://www.random.org/lists/ was used for randomization. All 45 subjects were included in the randomization and the first 30 listed were then placed into the treatment group.

Subjects in the treatment group received 20-64 units of onabotulinumtoxinA (BOTOX Cosmetic, Allergan plc, Coolock, Ireland), in the upper third of the face including glabella lines (GL), forehead lines (FL), and lateral canthal lines (LCL). Subjects returned after 2 weeks and were assessed by the investigator to determine whether or not optimal cosmetic result (OCR) was achieved and that subjects experienced a reduction of at least one point on the FWS. If OCR was achieved, subjects completed the same FACE-Q scale and happiness questionnaire they performed at baseline. They also completed the FACE-Q Satisfaction with Outcome[7] and a questionnaire comparing their perceived results of the onabotulinumtoxinA treatment compared to their prior neurotoxin treatments.

If additional correction was determined to be needed, then touch up treatment of up to 20 units was administered to patients at the second visit. These subjects then returned 2 weeks later to complete the FACE-Q survey, subject happiness scale, and questionnaire comparing this neurotoxin treatment to previous treatments.

Subjects in the control group underwent a similar assessment. However, the control group was administered saline rather than onabotulinumtoxinA at their initial treatment. Investigators administered the FACE-Q eyebrow line appraisal and FACE-Q satisfaction surveys at 4 weeks post-baseline. At this 4-week follow-up, all subjects in the control group crossed over to the treatment group. Investigators administered the onabotulinumtoxinA treatment in the same technique as in the treatment arm. Once OCR was achieved, investigators assigned patients a final FWS score. Four weeks after treatment, subjects completed the FACE-Q eyebrow, survey FACE-Q self-satisfaction survey, subject happiness scale, and the comparison questionnaire to previous treatments.

All statistical analyses, summary tables, and data listings were performed using Excel (Microsoft Co., Redmond, WA, USA) software. Comparison of pre-treatment and post-treatment assessments including both patient-reported measures and physician-determined facial wrinkle score were analyzed through the use of paired *t*-tests. A two-sided p-value of 0.05 is considered statistically significant. Indices that were only completed after the final treatment and OCR are reported through descriptive means and standard deviations.

RESULTS

Forty-five subjects who have had neurotoxin treatment in the past were enrolled in this study, 30 in the treatment group and 15 in the control/crossover group. All patients completed the treatment and follow up period. Within the control group, 14 subjects identified as female, and one identified as male. The mean age of females in the control group was 49 years (range, 26-71 years) and the one male in the control group was 54 years of age. There were 26 females and 4 males enrolled in the control group. The females in the control group had a mean age of 48.8 (range, 24-67 years), and males similarly had a mean age of 49.2 (range, 49-63 years). The ages, along with other demographics, are listed in Table 1. The mean duration from previous neurotoxin treatment was 6 months, and all subjects were required to have not received neurotoxin within 20 weeks of the study. There were no complications among either groups throughout the study.

The senior author (S. H. D.) determined the FWS of all subjects at baseline and after final treatment. In the control group, the mean FWS score at baseline was 2.56 and remained unchanged following saline treatment. After the control group crossed over to the treatment arm to receive onabotulinumtoxinA, the FWS reduced from 2.56 to 0.47 ($P<0.0001$) following OCR. The treatment arm had a baseline FWS score of 2.57 and reduced to 0.45 ($p<0.0001$) following OCR.

The control group with 15 subjects received a mean of 1.03cc of saline at the first treatment. All 15 subjects received touch ups with an additional mean of 1.59cc of saline. At the crossover, the control subjects received a mean of 30 units of onabotulinumtoxinA combined to the GL, FL, and LCL. Fourteen subjects received touchups, with a mean of 13.8 units of onabotulinumtoxinA. A mean total of 42.9 units of onabotulinumtoxinA was used in the control group following crossover.

The treatment group of 30 subjects received 35.4 units of onabotulinumtoxinA at their first visit. There were 23 touch-ups with a mean of 14.1 units. A mean total of 46.2 units was used. When compared to the control group after crossover receiving onabotulinumtoxinA, there was no significant difference in mean volume at the initial treatment, $p=0.08$. The touch up total comparison between groups also showed no significant difference, $p=0.88$. When comparing total units among initial treatment and touch-up between the control group after crossover with onabotulinumtoxinA to the treatment group, the mean total units showed no significant difference, $p=0.27$.

Each subject completed the FACE-Q eyebrow appraisal assessment before and after treatment. The control group total FACE-Q score remained 23.58 out of a possible 28 at baseline and remained at 23.58 one month following saline treatment. Once the control group crossed over to the onabotulinumtoxinA treatment, FACE-Q scores reduced significantly in all categories as shown in Table 2.

In the onabotulinumtoxinA treatment group, all eight FACE-Q subscales showed significant improvement after treatment (P<0.0001). The total score in the treatment group improved from 23.66 pre-treatment to 10.56 post-treatment (P<0.0001). Specific mean scores for each item are reported in Table 2. There were no significant differences between the FACE-Q scores from the control group after crossing over to the treatment arm compared to the initial onabotulinumtoxinA treatment group.

Subjects completed a FACE-Q satisfaction questionnaire at their final visit. No significant differences between satisfaction scores were reported between treatment and control group following crossover to the treatment arm. The survey was not given to the control group following saline treatment. The treatment group reported an average FACE-Q satisfaction score of 21.43 and control group following crossover with onabotulinumtoxinA reported a score of 21.44. In comparison to previous neurotoxin treatments, 42/45 (93.3%) reported that they believed that the onabotulinumtoxinA treatment results had a faster onset during this round, while 2/45 reported that the time to results were equivocal to previous treatments and one reported slower onset. The equivocal result was originally in the control arm, while the slower reported result was in the treatment arm. Overall, patients reported a mean efficacy of 8.9 on a 10-point scale for the neurotoxin treatment. Subjects reported mean onset time of with onabotulinumtoxinA treatment of 2.87 days.

Overall, both groups reported significant changes in overall happiness/mood scores as judged on the SHS following onabotulinumtoxinA treatment. The control SHS pre-treatment score remained unchanged following saline treatment alone. Once the control group crossed over to the treatment arm with onabotulinumtoxinA, SHS scores improved significantly (Table 3). The treatment arm also reported significant improvements for all questions on the SHS (Table 3). A higher score in question 1-3 indicated greater happiness, while a lower score on question 4 indicated greater happiness. The control group SHS scores following onabotulinumtoxinA treatment compared to the treatment group scores showed no significant differences (Table 3).

DISCUSSION

To the authors' knowledge, this is the first trial to examine the direct effects of onabotulinumtoxinA treatment in non-naïve users on mood/happiness, self-satisfaction of appearance, and overall treatment satisfaction on non-naïve patients in relation to a pandemic. This study was performed during a once in a lifetime period of time during the COVID-19 pandemic. The scenario in which aesthetic clinics are closed and regular neurotoxin patients are unable to receive their treatment at the scheduled time may never occur again. Normally neurotoxin treatment effects last about 3-4

months in the upper face before experiencing a relapse of facial wrinkles[9,10]. Moreover, patients must continually return to the office for touch-up procedures and maintenance treatments. During initial stay-at-home orders, this was not possible as clinics were shut down around the country.

All of the study subjects presented to the clinic with a moderate-to-severe glabellar wrinkle score and experienced clinically and statistically significant reduction in the facial wrinkle score following onabotulinumtoxinA treatment. The control group that received placebo saline showed no changes in their FWS until after crossover and receiving onabotulinumtoxinA. These results support previous evidence regarding the efficacy of neurotoxin for treatment of glabellar lines, lateral canthal lines, and forehead line[11-14].

Some of the most important outcomes of aesthetic treatment are not only clinical improvement of a treatment's effects, but also the patient's self-reported mood/happiness, satisfaction, and appraisal of treatment. Our results demonstrated a significant increase in patient mood/happiness following onabotulinumtoxinA treatment (Table 3). The control group did not have an increase in happiness with placebo saline alone, indicating the powerful effect of onabotulinumtoxinA on their happiness This is a meaningful result particularly in the setting of the COVID-19 pandemic which has placed numerous stressors on patients.

Previous studies have demonstrated the powerful effects neurotoxins have on improving quality of life, self-esteem, and even as a treatment for depression.[15,16] Many studies trial neurotoxin treatments on naïve subjects. This current study demonstrated that regular, non-naïve, uses of neurotoxin will continue to have an increase in mood/happiness, self-satisfaction of appearance, and overall treatment satisfaction, despite an ongoing pandemic. It would not be surprising that many patients will have decreased moods during the pandemic due to the long-term social isolation and distancing. This study was able to distinguish from an elevation in mood/happiness between the neurotoxin treatment or by the simple fact that the aesthetic office had been reopened through the use of the placebo saline injection. The saline did not increase mood/happiness, self-satisfaction of appearance, or overall treatment satisfaction. Once given onabotulinumtoxinA, all of these increased significantly. This demonstrates that easing of COVID-19 restrictions alone did not improve patient happiness and self-satisfaction of appearance, or overall treatment satisfaction. Thus, these increases, came from the onabotulinumtoxinA treatment.

Our study results demonstrated the improvement in patient-reported FACE-Q eyebrow appraisal compared to placebo. The control group in this study reported no changes from baseline in their eyebrow appraisal scores following administration of the saline placebo. After cross-over and administration of the onabotulinumtoxinA treatment, the control group reported improvements similar to the primary treatment group across all criteria of eyebrow appraisal.

Charles Darwin first noted the link between facial expression and mood in his seminal work in 1872[17]. The "omega" sign, a term he coined to describe the contraction of the corrugator muscles, was associated with melancholy and a depressed mood. After its disappearance, subject mood improved without the associated melancholic features[17]. Since Charles Darwin first made this observation, it has been termed the facial feedback hypothesis and has become an important field of interest in psychology[18] and aesthetic medicine. Injection of neurotoxin to paralyze the upper face, including the GL, FL, and LCL, may increase mood by acting on this effect, as demonstrated in this study. The paralysis of these muscles prevents extended periods of a contracted upper facial region, inhibiting the effects of facial feedback. This effect has been previously reported in the literature, as the treatment of facial lines has been shown to self-esteem and mood[14].

As of July 27, 2020, 31 states had instituted mask mandates during the COVID-19 pandemic[19-21]. These mask mandates were implemented at different times and met with various levels of public sentiment[21-23]. In Illinois, the location of the senior author's practice, this mask mandate was issued beginning May 1, 2020 and remains in place at the time of this writing on December 28, 2020[24]. Masks cover one of the most powerful manifestations of humans, one that conveys an abundance of information regarding the individual. For many, the upper facial region is an area of extra importance in the midst of the pandemic, as it is one of the only regions of the face still visible to the public[25]. The upper region has been shown to correlate with the emotions of anger, sadness, and fear whereas happiness is often recognized by an observer in the lower half of the face[26]. When everyone is wearing a mask, our ability to detect negative emotions such as frowning increases, inducing a similar feeling in the individual. Paralysis of the upper glabellar region with neurotoxin may induce a greater sense of positive emotion due to the inability to gauge negative facial emotions.

Subjective evaluations such as in this study, have several limitations that deserve mentioning. The study was performed at a single site. The small sample with predominantly Caucasian female subjects is noted and further study is warranted, though the unique time period of clinic shutdowns has passed in most areas of the country.

CONCLUSIONS

OnabotulinumtoxinA treatment to the upper face in the midst of the COVID-19 pandemic was found to increase patient happiness, self-satisfaction with appearance, and overall treatment satisfaction. As the COVID-19 pandemic continues, aesthetic providers can offer the benefit of neurotoxin treatment to elevate mood/happiness and provide a sense of normalcy to our patients during these stressful times.

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Figure Legend

Figure 1. A 52-year-old female (A) before and (B) 2 weeks after OnabotulinumtoxinA injection control, maximum frown.

Table 1. Subject Demographics

	Treatment group	Control group
Gender (%)		
Males	4 (13.3)	1 (6.7)
Females	26 (86.7)	14 (93.3)
Age, mean (range, y)		
Males	49.2 (49-63)	54.0 (54)
Females	48.8 (24-67)	49.0 (26-71)
Race/Ethnicity (%)		
Caucasian	27 (90)	12 (80)
Hispanic American	3 (10)	2 (13.3)
Asian American	0 (0)	1 (6.7)

Table 2. FACE-Q Appraisal of Eyebrow Lines Scores

	Control group following crossover with OnabotulinumtoxinA treatment			Treatment group		
FACE-Q question	Mean pretreatment	Mean posttreatment with OnabotulinumtoxinA	p-value	Mean pretreatment	Mean posttreatment with OnabotulinumtoxinA	p-value
Question A	3.26	1.44	<0.0001	3.25	1.43	<0.0001
Question B	3.40	1.47	<0.0001	3.41	1.48	<0.0001
Question C	3.28	1.42	<0.0001	3.27	1.41	<0.0001
Question D	3.33	1.53	<0.0001	3.36	1.52	<0.0001
Question E	3.35	1.51	<0.0001	3.36	1.52	<0.0001
Question F	3.44	1.56	<0.0001	3.45	1.57	<0.0001
Question G	3.53	1.65	<0.0001	3.55	1.63	<0.0001
Total	23.58	10.58	<0.0001	23.66	10.56	<0.0001

Table 3. Subject Happiness Scale (SHS) Scores

	Control group following crossover with OnabotulinumtoxinA treatment			Treatment group			Control post OnabotulinumtoxinA vs treatment arm
SHS Item	Mean pretreatment	Mean posttreatment with OnabotulinumtoxinA	p-value	Mean pretreatment	Mean posttreatment with OnabotulinumtoxinA	p-value	P-value
Question 1	6.0	6.6	0.007	5.43	6.21	0.01	0.06
Question 2	6.08	6.53	0.05	5.54	6.21	0.008	0.10
Question 3	5.77	6.33	0.022	5.07	6.18	0.00005	0.51
Question 4	2.67	1.6	0.026	3.21	1.75	0.00009	0.72

Figure 1A

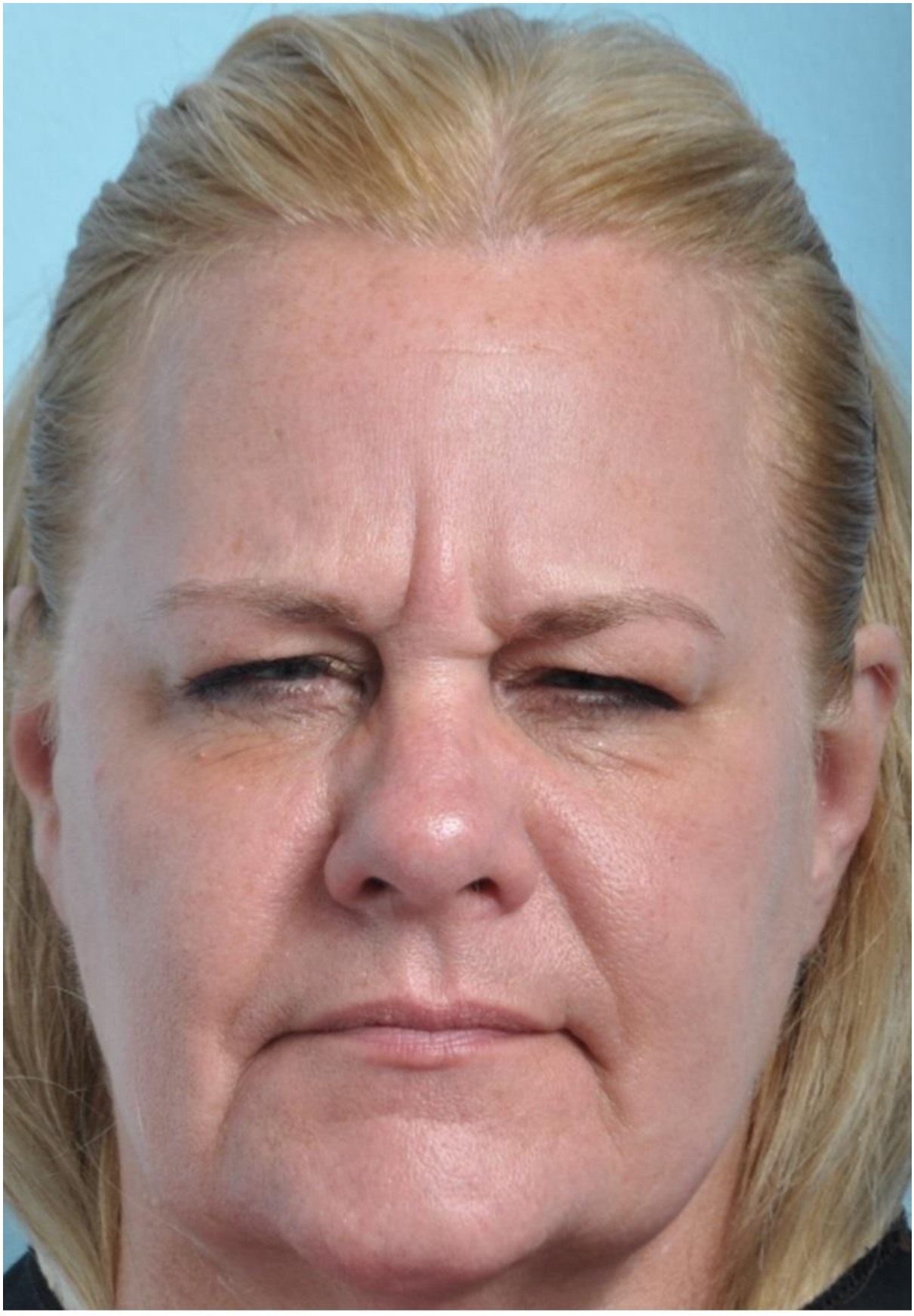

Figure 1B