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Complications and Anatomical Considerations in Botulinum Neurotoxin Type A Injections for Upper Face Rejuvenation: A Systematic Review

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ABSTRACT

Botulinum neurotoxin type A (BoNT-A) is widely utilized in aesthetic medicine for the treatment of dynamic rhytides in the upper face. Despite its efficacy, the intricate anatomy of the upper face poses significant challenges, with potential complications ranging from transient injection-site reactions to more severe outcomes such as eyelid ptosis and facial asymmetry. This systematic review aims to provide a comprehensive analysis of the complications associated with BoNT-A injections in the upper face, focusing on the interplay between anatomical variations, injection techniques, and patient-specific factors. By synthesizing current clinical evidence, this review highlights the importance of precise anatomical knowledge, standardized injection protocols, and injector expertise in minimizing adverse effects. Furthermore, it offers evidence-based recommendations to enhance the safety and efficacy of BoNT-A treatments, ensuring optimal aesthetic outcomes while mitigating risks.

Keywords: botulinum neurotoxin, botulin toxin, upper face, aesthetic medicine, injection complications

Introduction

Botulinum neurotoxin type A (BoNT-A), derived from Clostridium botulinum, represents one of the most extensively utilised agents in both therapeutic and aesthetic medicine[1], [2] . Initially developed for the management of neurological disorders, its application has expanded significantly, particularly within the field of facial aesthetics, where it serves as a cornerstone of non-surgical rejuvenation [2]. Commercially, it is available under multiple formulations, including onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®), and prabotulinumtoxinA (Jeuveau®), each exhibiting distinct pharmacokinetic properties influenced by their respective complexing proteins and purification processes [3], [4]. Such variations necessitate a precise understanding of their differing diffusion patterns, potency units, and clinical efficacy to ensure optimal patient outcomes.

The therapeutic mechanism of BoNT-A is well characterized, through inhibition of acetylcholine release at the neuromuscular junction, it induces temporary chemodenervation, resulting in localised muscle relaxation [5]. This neuromodulatory effect underpins its efficacy in addressing a wide array of medical conditions, including dystonia, spasticity, chronic migraines, and hyperhidrosis. In aesthetic medicine, its primary indication lies in the attenuation of dynamic rhytides (wrinkles formed as a consequence of repetitive facial muscle contractions) by selectively diminishing the activity of targeted musculature. The U.S. Food and Drug Administration (FDA) first sanctioned BoNT-A for cosmetic use in 2002, specifically for the treatment of glabellar lines, with subsequent approvals encompassing forehead wrinkles, periorbital rhytides, and other expression-related facial lines [1], [2], [3], [6]. Today, BoNT-A remains unparalleled in its capacity to achieve subtle yet effective facial rejuvenation, offering a minimally invasive alternative to surgical interventions.

The anatomical complexity of the upper face, however, presents considerable challenges in the administration of BoNT-A, necessitating a comprehensive understanding of the underlying musculature, neurovascular structures, and their intricate interplay [6], [7]. Key muscular targets include the frontalis, corrugator supercilii, and orbicularis oculi, each contributing to distinct facial expressions [8]. While the precise delivery of BoNT-A enables effective attenuation of hyperdynamic muscle activity, improper injection technique or a failure to account for individual anatomical variations may precipitate undesirable effects, ranging from transient complications, such as ecchymosis or asymmetry, to more pronounced adverse

outcomes, including eyelid or eyebrow ptosis, excessive diffusion, or unintended paralysis of adjacent musculature. Given the proximity of critical neurovascular structures, such as the supraorbital and supratrochlear nerves, as well as branches of the facial artery, the potential for iatrogenic complications is not insignificant[9], [10], [11], [12].

Although BoNT-A is widely regarded as safe when administered by experienced practitioners, the expanding prevalence of its cosmetic use has brought increased scrutiny to the nature and frequency of treatment-related complications. Systematic reviews and meta-analyses indicate that adverse events, while often mild and self-limiting, remain an inherent consideration in BoNT-A administration, with headache, local skin reactions, and transient facial weakness among the most commonly reported sequelae [2], [13], [14], [15], [16]. However, inconsistencies in the reporting and classification of such complications in the literature pose challenges in establishing definitive risk stratifications. Moreover, as patient demand for minimally invasive aesthetic procedures continues to rise, the necessity for standardised protocols and evidence-based injection techniques becomes increasingly imperative.

This review, therefore, aims to provide a rigorous and anatomically grounded analysis of the potential complications associated with BoNT-A injections in the upper face. By synthesising current clinical evidence and refining established injection methodologies, this article seeks to enhance the safety and predictability of BoNT-A treatments, equipping practitioners with the necessary knowledge to mitigate risks while maximising aesthetic and functional outcomes. Through an exploration of both common and less frequently encountered complications, we endeavour to delineate best practices that uphold the highest standards of patient care in aesthetic medicine.

Materials and methods

A systematic review of the literature was conducted, encompassing peer-reviewed articles, clinical trials, and meta-analyses published between 1992 and 2024. Databases such as PubMed, Scopus, and Google Scholar were searched using keywords including "botulinum toxin," "upper face," "complications," and "aesthetic medicine." Studies were selected based on their relevance to BoNT-A injections in the upper face, with a focus on complications, anatomical considerations, and injection techniques. Only articles published in English were included. Data were extracted and synthesized to identify common complications, risk factors, and best practices. Case reports and expert recommendations were also reviewed to provide a

comprehensive understanding of the subject. The findings were analyzed to develop evidence-based guidelines for optimizing BoNT-A administration in the upper face.

Discussion

A precise and comprehensive understanding of facial musculature is essential for effective BoNT treatment, as the unique anatomical and functional properties of these muscles dictate both aesthetic outcomes and potential complications. Unlike other skeletal muscles, those responsible for facial expression are intricately connected to the overlying cutaneous tissue through the superficial musculoaponeurotic system (SMAS), directly influencing both dynamic and static facial lines [6]. The interplay between elevators and depressors determines brow positioning and overall facial harmony, with muscle action occurring across vertical, horizontal, and sphincteric planes[17], [18]. The forehead is primarily influenced by the frontalis muscle, an elevator, whereas the glabellar and periocular regions are dominated by depressors such as the corrugator supercilii and orbicularis oculi (Table 1). Given that rhytids form perpendicularly to underlying muscle fibers, precise injection technique, targeting the appropriate muscle at the correct depth, is paramount in achieving the desired modulation of facial expression[8], [19]. Inaccurate injections, whether too superficial or too deep, risk unintended muscle involvement, potentially counteracting the intended effect. Therefore, patient-specific assessments that consider muscle tone, baseline activity, and facial symmetry are critical for optimising BoNT efficacy while minimising adverse effects [2], [20].

Table 1: Key muscle groups in the upper face and their respective actions

Region	Elevators	Depressors
Forehead	Frontalis	None
Glabellar	None	Corrugator supercilii, Procerus, Depressor supercilii
Periocular	Frontalis	Orbicularis oculi, Depressor supercilii

The frontalis muscle, the primary elevator of the upper face, is a paired, flat, sheet-like structure that originates from the galea aponeurotica [8]. It travels at a consistent depth beneath the forehead skin, approximately 3-5 mm, before inserting into the dermis above the eyebrows[18].

It plays a pivotal role in brow elevation and the formation of horizontal forehead lines [17], [21]. Variations in its anatomical configuration influence its function and response to BoNT treatment [22]. Four distinct configurations of the frontalis muscle have been described, each presenting unique considerations for BoNT injection, as outlined in Table 2. Improper injection into the frontalis, particularly without addressing its antagonistic depressor muscles, may result in unopposed brow depression, leading to complications such as brow ptosis or exaggerated asymmetry. Tailored injection techniques that balance these opposing forces are essential for achieving natural-looking results [6], [22].

Table 2: Anatomical variations of the frontalis muscle

Type	Configuration
I	Continuous bellies spanning the midline, producing straight horizontal wrinkles.
II	V-shaped bellies separated by an aponeurotic projection, forming gull-wing-shaped wrinkles.
III	Medial bellies restricted to the central forehead, leading to short vertical wrinkles.
IV	Lateral bellies with medial separation, creating isolated lateral columns of wrinkles.

The glabellar complex comprises the corrugator supercilii, procerus, and depressor supercilii, which collectively depress the medial brow and contribute to the formation of vertical and transverse rhytids[17]. The corrugator supercilii, the primary muscle responsible for vertical glabellar lines, originates from the superciliary arch and extends into the skin above the medial eyebrow. Due to its layered position, deep medially and superficial laterally, precise toxin placement is critical to avoid unintended effects. The muscle measures 2-3 mm in thickness, with the thickest portion located 19 mm from the nasion, between vertical lines drawn from the medial canthus and mid-pupillary region [18]. Injections should be placed at a depth of 3-5 mm to avoid affecting surrounding structures, such as the levator palpebrae superioris, which could result in eyelid ptosis. Tailored injection strategies are essential, as a broader muscle may require a more dispersed injection pattern, while a narrower muscle necessitates targeted dosing.

The depressor supercilii, a muscle whose classification as a distinct entity or as an extension of the orbicularis oculi remains debated, is responsible for lowering the medial brow [21]. It

originates from the frontal process of the maxillary bone, often arising as two separate heads, typically located 1 cm above the medial canthal tendon[23]. The muscle inserts approximately 13-14 mm superior to the medial canthal tendon, lateral to the insertion of the corrugator supercilii. When targeted with BoNT, it can contribute to enhanced brow elevation, particularly when treated in conjunction with the corrugator and procerus. However, inadvertent diffusion of the toxin into the frontalis can compromise its lifting effect, highlighting the importance of precise control over injection depth and volume[17], [23].

The procerus is a pyramid-shaped muscle located at the midline between the brows, originating from both the superficial and deep layers at the nasal bone and cartilage. It inserts into the skin of the lower forehead between the eyebrows and into the frontalis muscle. The majority of its fibers form part of the hourglass-shaped superficial portion, which narrows at the level of the medial palpebral ligament before fanning out above and below[8], [18], [20]. The vertically oriented fibers of the procerus depress the medial eyebrow, contributing to the formation of transverse wrinkles at the nasal root and horizontal rhytids. BoNT injections in this region are often combined with treatment of the corrugator supercilii to achieve a balanced softening of the glabellar area. However, excessive weakening of the procerus can lead to a flattening of brow dynamics, resulting in a heavy or unnatural appearance[20].

Encircling the eye, the orbicularis oculi plays a crucial role in eyelid closure and brow positioning. It consists of three functional regions: orbital, responsible for forceful blinking and crow’s feet formation; palpebral, facilitating gentle eyelid closure; and lacrimal, assisting with tear drainage. BoNT is commonly used to soften lateral canthal lines ("crow’s feet") and achieve a subtle lateral brow lift. However, excessive weakening of the orbital portion can impair eyelid closure or result in unnatural brow positioning, highlighting the need for careful dose calibration[24], [25].

Directly opposing the orbicularis oculi, the levator palpebrae superioris (LPS) is the primary muscle responsible for eyelid elevation. The LPS, a triangular muscle about 40 mm long, extends from the orbital apex to the upper eyelid and plays a key role in eyelid elevation. It directly opposes the orbicularis oculi, which controls eyelid closure[24]. Since the LPS is innervated by the superior branch of the oculomotor nerve (cranial nerve III), unintended diffusion of BoNT can weaken or inactivate it, leading to ptosis. Additionally, Müller's muscle, a smaller smooth muscle located just beneath the LPS, provides secondary support for eyelid elevation. It is controlled by the sympathetic nervous system and can raise the lid by an extra

1–2.5 mm. This muscle's function explains why certain eye drops, like apraclonidine, can temporarily correct mild ptosis by stimulating contraction[26].

Beyond muscular anatomy, the orbital septum serves as a critical fibrous barrier separating the superficial and deep orbital compartments. It houses essential neurovascular structures, including the supraorbital, supratrochlear, and lacrimal arteries. The supraorbital pedicle, which exits via either a notch (74%) or a foramen (26%), presents an anatomical variation that may influence the risk of toxin migration into adjacent structures, such as the LPS, further underscoring the need for precise injection techniques[15], [25]. Clinically, assessing upper eyelid position is crucial for identifying BoNT-related complications. The normal upper eyelid margin sits 1–2 mm below the upper limbus, while the palpebral fissure height, the vertical distance between the upper and lower eyelid margins, averages 11–12 mm. These parameters help monitor potential toxin-induced changes, such as lid ptosis or retraction treatments[7], [15], [27], [28].

A thorough understanding of upper-face anatomy is essential for optimising BoNT treatments while minimising risks. The interplay between the orbicularis oculi, levator palpebrae superioris, and supporting structures determines eyelid position and brow elevation, meaning imprecise injection depth, dosage, or diffusion can lead to functional and aesthetic complications.

Side Effects of Botulinum Toxin in Upper Face Treatments

The safety profile of BoNT in upper face rejuvenation remains a topic of considerable interest, with reported complication rates varying across studies due to differences in injection protocols, toxin formulations, practitioner expertise and patient demographics (Table 3).

Table 1: Adverse Event Rates in Upper Face BoNT Treatments

Study	Sample Size	Overall Adverse Event Rate	Blepharoptosis (%)	Brow Ptosis (%)	Bruising (%)	Headache (%)	Serious Adverse Events (%)
Kashkouli et al. (2014)	845	2.6%	0.3%	0.2%	1.8%	0.2%	0%

Zargaran et al. (2022)	4268	16%	Not reported	Not reported	Not reported	Not reported	1.6%
Brin et al. (2023)	5298	35.8% - 42.1%	1.0%	0.6%	Not reported	Not reported	1.6%
Cavallini et al. (2021)	8787	Not reported	2.5%	3.1%	5.0%	16.8%	Not reported

In a retrospective study by Kashkouli et al (2014) involving 845 subjects undergoing 18 point a BoNT upper face rejuvenation, the overall adverse event incidence was notably low at 2.6%[29]. This protocol targeted forehead creases at four points, frown lines at five points, bunny lines at one point, crow's feet at four bilateral points and lower eyelid creases at four bilateral points, with follow-up visits at 10 to 14 days for touch up injections, primarily addressing eyebrow asymmetry in 8% of cases. The majority of adverse events were bruising at 1.8%, followed by blepharoptosis at 0.3%, residual eyebrow asymmetry at 0.2% and headache at 0.2%. Notably, adverse events were significantly more frequent in younger subjects under 40 years, those receiving touch ups and during the injector's first two years of experience, particularly for bruising [29].These findings contrast with broader analyses, such as the meta-analysis by Zargaran et al (2022), which reported a 16% complication rate across 4268 botulinum toxin A sessions, including headaches and localised skin reactions and Brin et al (2023), who observed adverse events in 35.8 to 42.1% of 5298 participants, with eyelid ptosis at 1.0% and brow ptosis at 0.6% as notable complications [2], [13]. The lower adverse event rate in Kashkouli et al's study may reflect the standardised 18 point protocol, precise anatomical targeting and early touch up interventions to correct asymmetry, which likely minimised toxin diffusion and prolonged muscle weakness.

Blepharoptosis rates in Kashkouli et al's cohort, at 0.3%, were markedly lower than the 2.5% reported in Cavallini et al's (2021) systematic review of 8787 subjects, which identified brow ptosis in 3.1% of cases and highlighted a dose dependent risk, with rates reaching 21% for high dose BoNT [14].Similarly, Sethi et al (2020) reported eyelid ptosis at 0.71% and brow ptosis at 0.98% in their cohort, aligning more closely with Brin et al's (2023) findings of 1.0% eyelid ptosis than with Kashkouli et al's results. These disparities may stem from differences in toxin type, as BoNT was used in Kashkouli et al's study compared to BoNT in Cavallini's review, as

well as injection technique. For instance, Kashkouli et al avoided medial brow injections, a known risk factor for ptosis, and utilised lower eyelid crease injections, which may reduce compensatory frontalis overactivation. Headache incidence in Kashkouli et al's study, at 0.2%, was also strikingly lower than the 16.8% reported by Cavallini et al (2021), potentially due to differences in patient reporting thresholds or the transient nature of headaches, which may resolve before follow up visits.

Bruising, the most common adverse event in Kashkouli et al's study at 1.8%, occurred less frequently than the 5% rate noted in Cavallini et al's review [14].This may reflect the use of smaller gauge needles or meticulous avoidance of superficial vasculature in the 18 point protocol. However, bruising was significantly associated with injector inexperience during their first two years of practice and younger age under 40 years corroborating Zargaran et al's (2022) observation that less experienced practitioners report higher complication rates of 20 to 30% [13]. Younger patients' higher muscle activity or thinner skin may predispose them to vascular trauma. Other localised adverse events, such as eyelid heaviness up to 4.7% and forehead tightness at 5.9% noted by Cavallini et al (2021), were not explicitly reported by Kashkouli et al, though residual eyebrow asymmetry at 0.2% persisted even after touch ups, emphasising the challenge of balancing muscle relaxation in dynamic facial regions[13], [14], [29].

Serious adverse events, though rare, were absent in Kashkouli et al's cohort but reported in Brin et al's (2023) meta-analysis at a rate of 1.6%, including basal cell carcinoma at 0.2% and myocardial infarction at 0.1% [2]. These systemic events are unlikely directly linked to botulinum toxin A and may instead reflect comorbidities in older populations or incidental findings. The absence of serious adverse events in Kashkouli et al's study further underscores the safety of abobotulinumtoxinA in standardised protocols when administered by trained practitioners.

The interplay of factors influencing adverse event risk, such as injector experience, patient age and injection technique, is evident across studies. While Kashkouli et al (2014) demonstrated that structured protocols and early touch ups mitigate complications, broader analyses highlight the risks of over injection, improper dosing and anatomical variability. For example, Brin et al (2023) observed higher serious adverse event rates in combined treatment areas, such as 2.7% for crow's feet and glabellar lines suggesting cumulative risks with multisite injections. Conversely, Kashkouli et al's low adverse event rate reinforces the value of precision in toxin

placement, particularly in high risk zones like the lower eyelid crease, which demands careful technique to avoid orbicularis oculi weakening[2], [29].

Injection-Site Reactions

Building upon the established safety profile of botulinum toxin A in upper face rejuvenation, injection-site reactions warrant detailed analysis due to their variability in presentation and underlying mechanisms. While haematoma and ecchymosis dominate as the most frequent complications, their pathophysiology extends beyond superficial capillary disruption [9]. Haematomas arise from inadvertent puncture of deeper vessels, particularly in regions with dense vascular networks such as the glabella and lateral canthal areas[30]. This risk is amplified by anatomical variations, such as the presence of the angular artery near the medial canthus, which may be obscured in patients with thinner subcutaneous tissue. Ecchymosis, though often dismissed as a transient cosmetic concern, can persist for 7–14 days in patients with coagulopathies or those taking anticoagulant therapy, necessitating pre-treatment counselling [9]. The correlation between toxin volume and vascular injury, as highlighted in recent studies, suggests that higher dilution volumes may increase tissue distension and capillary shear stress, exacerbating bruising even with meticulous technique [9]. While topical agents like *Arnica montana* are widely advocated, their efficacy remains contentious [31].

Post-injection headaches, though typically transient, exhibit a bimodal temporal pattern. Immediate-onset headaches (within 24 hours) are linked to periosteal trauma or intramuscular haematoma formation, particularly with deep injections targeting the frontalis or corrugator origins[32]. Delayed-onset headaches (3–7 days post-treatment), observed in 1.2% of cases, may reflect compensatory muscle hyperactivity in untreated areas or neurogenic inflammation. Notably, a subset of patients with pre-existing tension-type headaches or migraines report prolonged symptoms lasting 4–6 weeks, necessitating multidisciplinary management involving neurologists [33].

Localized swelling, or oedema, is an uncommon side effect of BoNT injections in the upper face, with incidence rates typically reported below 0.5%. Specific studies have documented the occurrence of erythema at 0.06% and mild oedema at 0.036% [12]. Eyelid oedema, a more prominent variant, has an incidence ranging from 0.4% to 1.4% and is influenced by factors such as thinner skin, dermatochalasis, or low periocular muscle tone. Certain ethnic groups, such as Asian populations, are at a higher risk due to anatomical differences[12], [32]. The likelihood of oedema increases with over-dilution of the toxin, improper injection techniques,

or placement near the orbital septum, which can lead to unintended diffusion into surrounding tissues.

In rare instances, recurrent localized swelling can occur, as seen in a 50-year-old female patient who experienced erythema, oedema, and tenderness between the eyebrows 10 days after BoNT injections. This reaction resolved spontaneously but recurred twice over the following month[34]. It was likely exacerbated by lymphatic disturbances in regions where higher doses were administered, emphasizing the importance of anatomical variations and post-injection care[9], [12], [34]. Severe reactions, though exceptionally rare, demand heightened vigilance. Anaphylaxis, occurring in 0.003% of cases, frequently correlates with latex-containing syringe plungers or stabilisers like human serum albumin rather than the neurotoxin itself [2], [9]. A 2023 pharmacovigilance analysis identified seven cases of BoNT-associated pneumonia, all in patients with pre-existing dysphagia who received concomitant cervical injections, highlighting the importance of systemic symptom monitoring beyond the treatment site [2]. Infectious complications, while theoretically preventable, continue to be reported in 0.007% of cases, predominantly introduced through contaminated reconstitution solutions or improper skin preparation [9], [35].

Facial Asymmetry and Ptosis

Facial asymmetry, a potential complication of BoNT injections, often arises from improper injection techniques, uneven dosing, or individual anatomical variations. A common issue is the "Spock brow," or ‘Memphisto’, characterised by an exaggerated lateral eyebrow arch due to over-relaxation of the central frontalis muscle while the lateral fibres remain active[4]. This condition, often linked to imbalanced toxin distribution, can be corrected by injecting additional toxin into the hyperactive lateral frontalis[12]. Such asymmetries are more prevalent in treatments performed by less experienced practitioners, with up to 50% of cases reported in these settings[12]

In older patients, pre-existing asymmetries, such as variations in brow position or eyelid height, can exacerbate complications. Weakening of the frontalis muscle may contribute to ptosis or eyelid drooping, particularly in those who rely on compensatory brow elevation for unobstructed vision [13]. Zargaran et al. (2022) noted that frontalis-related asymmetries occur in 3.3% of cases, with a higher incidence among less experienced injectors [13]. These issues

can often be rectified with touch-up treatments, emphasising the importance of thorough pre-treatment assessments and individualised dosing plans.

Eyebrow ptosis

Eyebrow ptosis, frequently arising from undue relaxation of the frontalis muscle, is a common complication, particularly when injections are administered perilously close to the supraorbital rim [7]. This condition often leads to a drooping brow, especially when the functionality of the frontalis muscle is impaired. The incidence of eyebrow ptosis varies from less than 1% to 5%, contingent upon the injection techniques employed and patient-specific variables [36]. Contributing factors include improperly chosen injection sites, excessive dosing, and suboptimal patient selection. To mitigate these risks, it is advisable to inject at a minimum distance of 2–3 cm above the supraorbital margin or maintain a separation of 1.5–2 cm above the eyebrow, thereby preserving the function of the frontalis muscle in the upper forehead[37]. Moreover, a balanced approach in treating both the glabellar and forehead regions is crucial to prevent unopposed depressor action, which can culminate in ptosis. Noteworthy is the fact that the toxin may migrate through the orbital septum, potentially causing a weakening of the levator palpebrae superioris muscle [7]. This complication is typically observed when the toxin is injected near the supraorbital margin along the mid-pupillary line or when higher quantities of the toxin are utilized. Ptosis may manifest within 7–10 days post-injection and can persist for 2–4 weeks or even longer[38]. A study evaluating 25 patients treated with BoNT/A for forehead rhytides reported a mean eyebrow ptosis of 2.3 mm in 22 individuals, while no cases of eyelid ptosis were observed. The brow ptosis was attributed to frontalis over-relaxation from injections administered too close to the supraorbital rim. Implementation of preventive strategies, including injections further from the supraorbital margin, successfully preserved frontalis function and mitigated the risk of ptosis in subsequent cases[7].

Eyelid ptosis

Eyelid ptosis (blepharoptosis), a recognized complication of BoNT injections, occurs due to unintended diffusion of the neurotoxin to the levator palpebrae superioris muscle, leading to temporary paralysis and reduced eyelid height. The incidence varies depending on injector experience, with higher rates observed among less experienced practitioners. A review of multiple studies estimated an average incidence of 2.5%, with a declining trend over time as techniques improve[25]. This complication manifests 2–10 days post-injection and resolves within 2–4 weeks, although some cases may persist longer [27], [28]. Risk factors include

injection near the supraorbital rim, excessive toxin dilution, and patient-specific factors such as age and pre-existing dermatochalasis, which exacerbate susceptibility [38].Preventive strategies involve precise injection techniques, avoiding the medial corrugator tail near the levator muscle, and applying post-injection pressure to limit toxin diffusion[27]. Therapeutically, alpha-adrenergic agonists such as apraclonidine (0.5%) and brimonidine (0.15%) are first-line options, stimulating Müller's muscle for temporary elevation of 1–2 mm, with reapplication every 6–8 hours [38]. Emerging alternatives, such as brimonidine gel, have demonstrated efficacy with reduced systemic absorption. Case reports illustrate these approaches, Alotaibi et al. (2022) documented a 35-year-old patient successfully managed with 0.33% brimonidine gel, achieving a 2-mm lift within an hour and no adverse effects[28]. Similarly, Kkaya et al. (2015) reported significant improvement in a patient treated with apraclonidine drops, resolving ptosis and accompanying mydriasis within days[39]. In a severe case, Musharbash & Chakra (2024) described successful recovery of persistent ptosis following secondary BoNT injections in the pre-tarsal region[27]. These cases underscore the transient nature of BoNT/A-induced ptosis and highlight both established and innovative treatments for optimizing outcomes.

Other Ophthalmic Complications

Ophthalmic complications arising from BoNT injections in the upper face, though frequently transient, represent a clinically significant subset of adverse events, accounting for approximately 24% of BoNT-related complications reported to regulatory authorities such as the FDA[40]. These sequelae range from benign manifestations, including dry eye and epiphora, to functionally consequential outcomes such as diplopia, lagophthalmos, and, albeit rarely, transient vision loss [14]. While the majority resolve spontaneously within 1–12 weeks as the pharmacological effects of the toxin diminish, their potential to induce patient morbidity necessitates rigorous adherence to anatomical precision and prophylactic protocols[41].

The aetiology of these complications predominantly centres on the unintended diffusion of BoNT into periocular or intraocular structures, a phenomenon exacerbated by suboptimal injection techniques, such as excessive dosing, incorrect needle depth, or proximity to high-risk anatomical zones, or pre-existing patient factors, such as eyelid laxity, dermatochalasis, or compromised lacrimal function[40]. Preventive strategies universally emphasise meticulous technique, focusing on superficial administration using fine-gauge needles, for example, 30-gauge, adherence to safe distances from critical landmarks, for example, at least 1.5 cm lateral

to the orbital rim, and utilisation of the lowest effective doses, 2.5 to 5 units per site, diluted in sufficient volumes, for example, 10 units in 2 to 2.5 mL saline, to mitigate diffusion risks. Conservative management, including ocular lubricants, prismatic correction, or temporary occlusion, suffices for most cases, with surgical intervention reserved for refractory malposition, such as ectropion or orbital fat herniation.

Diplopia, occurring in 1.7 % and accounting for up to 64 % of reported ophthalmic adverse events of periocular BoNT applications, exemplifies the interplay between toxin diffusion and functional anatomy[38]. Lateral rectus involvement during crow's feet treatments, as demonstrated in cases by Dolar Bilge et al. (2016) and Khan et al. (2023), underscores the necessity of lateral orbicularis raphe targeting and toxin dilution to avert extraocular muscle paresis[10], [11]. Similarly, lagophthalmos, frequently concomitant with dry eye syndrome, 64 % incidence post-injection, arises from orbicularis oculi paralysis, particularly when injections encroach upon the preseptal rather than pretarsal muscle regions[7]. Xerophthalmia, or dry eye, is a potential complication of BoNT injections, particularly when targeting the periocular region. This condition arises from reduced tear production due to BoNT's effect on lacrimal gland function or periocular musculature, which can disrupt the blink reflex and exacerbate tear film instability[40], [42]. The reported incidence of dry eye following BoNT injections is approximately 1 to 3 %, with a higher prevalence in patients with pre-existing dry eye symptoms or anatomical predispositions. Management strategies here prioritise corneal protection, with severe cases warranting induced ptosis via levator palpebrae injections, an approach validated by Yücel et al. (2012) [43].

Lower eyelid ectropion, though rare, 0.5 to 1 % incidence, disproportionately affects elderly patients or those with inherent laxity, necessitating avoidance of pretarsal injections and judicious lateral placement. Orbital fat protrusion, a less-documented complication, manifests in predisposed individuals due to orbicularis weakening and septal laxity, often necessitating surgical correction if conservative measures, for example, lymphatic massage, prove inadequate[42]. Epiphora, observed in 2 % of cases, stems from medial orbicularis paralysis impairing lacrimal pump function, while transient vision loss, exceedingly rare, less than 0.1 %, yet alarming, is hypothesised to result from vascular compromise or direct toxin effects on optic nerve microvasculature[42], [44].

Conclusion

Botulinum neurotoxin is a highly effective therapeutic agent for upper face rejuvenation, offering significant aesthetic benefits with a generally favorable safety profile. However, the complex anatomy of the upper face, characterized by the interplay of multiple muscle groups and neurovascular structures, necessitates a meticulous approach to injection techniques. This review underscores the importance of anatomical precision, individualized treatment planning, and injector expertise in minimizing complications such as ptosis, facial asymmetry, and ophthalmic adverse events. By adhering to standardized protocols and evidence-based practices, practitioners can enhance the safety and efficacy of BoNT-A treatments. Future research should focus on further elucidating the anatomical variations that influence treatment outcomes and developing comprehensive guidelines to address the evolving demands of aesthetic medicine. Ultimately, a thorough understanding of both the therapeutic potential and the risks associated with BoNT-A is essential for achieving optimal patient outcomes in upper face rejuvenation.

Disclosure

Author's contribution

Conceptualization: Maria Kąpa; Methodology: Maria Kąpa, Bartosz Szepietowski, Michał Wijata; Software: Jan Szustak, Anna Maria Wijata, Zuzanna Adriana Przybyłek-Stępień; Check: Maria Kąpa, Bartosz Szepietowski; Formal analysis: Maria Kąpa, Jan Szustak, Anna Maria Wijata; Investigation: Maria Kąpa, Zuzanna Adriana Przybyłek-Stępień; Resources: Maria Kąpa, Piotr Pasek ,Jan Szustak, Jakub Marek Kaźmierczak; Data curation: Bartosz Szepietowski, Anna Maria Wijata, Ryszard Bartosiński; Writing-rough preparation: Maria Kąpa, Zuzanna Adriana Przybyłek-Stępień; Writing-review and editing: Justyna Dutkiewicz , Michał Wijata, Jakub Marek Kaźmierczak; Visualization: Ewelina Rycerz, Wiktoria Mączyńska Ryszard Bartosiński; Supervision: Justyna Dutkiewicz; Project administration: Ewelina Rycerz, Wiktoria Mączyńska, Piotr Pasek

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The authors declare no conflict of interest.

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