Botulinum toxin in the management of facial paralysis

Purpose of review
Complete flaccid facial paralysis, as well as the synkinetic and hyperkinetic sequelae of partial recovery, has significant impact on quality of life. Patients suffer from functional deficiencies, cosmetic deformity, discomfort and social consequences leading to emotional distress. Despite an extensive and sophisticated array of available interventions for facial reanimation, most patients have persistent issues that require consistent follow-up. In long-term management, botulinum toxin (BT) injection remains a critical tool in the treatment of the facial paralysis patient, particularly in the case of synkinesis, hyperkinesis and imbalance. We review the recent scientific literature and highlight key principles and developments in the use of BT in the management of facial paralysis, including less common applications for acute facial paralysis, hyperlacrimation and pseudoptosis.

Recent findings
We reviewed the literature for the latest advances in the use of BT in facial paralysis, including applications and technique, as well as measurement tools and adjunct exercises. We also share our experience in treating our own patient population.

Summary
BT continues to be a well tolerated and effective tool in the long-term management of facial paralysis, specifically in treating synkinesis, imbalance and hyperkinesis, as well as hyperlacrimation and pseudoptosis. Consistent measurement tools and adjunct neuromuscular retraining are crucial in the successful deployment of BT. Controversy exists as to whether BT should be used to manage facial paralysis during the acute phase, and whether BT application to the nonparalyzed face can improve long-term recovery in the paralyzed side.

Keywords
Bell’s palsy, botulinum toxin, facial paralysis, hyperkinesis, synkinesis

INTRODUCTION
Facial paralysis with resultant permanent paresis and synkinesis presents tremendous management issues for the practitioner. Even in the case of Bell’s palsy, which has a favorable prognosis, up to 30% of patients will have incomplete functional or aesthetic recovery [1–3].

Botulinum toxin (BT) chemically denervates muscle by irreversibly blocking presynaptic acetylcholine release. After direct muscular injection, BT maintains effect until newly sprouted axon terminals regain synaptic contact with the muscle, typically occurring between 3 and 6 months posttreatment [2,4–6]. Since its first reported use in 1973 for the treatment of strabismus, BT has been successfully applied to a multitude of muscular disorders [4,5,7–11]. The use of BT for the treatment of synkinesis was first reported in the German literature in 1991, in the elimination of involuntary oro-ocular eye closure [12,13]. In recent years, BT has been increasingly employed in cases of facial imbalance, hyperkinesis and synkinesis in the setting of previous facial nerve injury [1,14–22]. Recent research has demonstrated the value of...
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KEY POINTS

- The lasting sequelae of partial facial paralysis can have a profound impact on patient quality of life.
- Botulinum toxin injection is a well tolerated and effective treatment for synkinesis, hyperkinesis and facial imbalance.
- Botulinum toxin can be effective in rarer sequelae of facial paralysis, including pseudoptosis and hyperlacrimation.
- Preliminary research suggests that botulinum toxin may be used in the acute phase of facial paralysis, and that nonparalyzed side botulinum toxin injections may improve the long-term recovery of the paralyzed side.
- Careful measurement, documentation and routine follow-up is key in the use of botulinum toxin in the treatment of facial paralysis.
- Patients should be offered neuromuscular feedback physical therapy, as these exercises are synergistic with botulinum toxin injections in improving synkinesis, hyperkinesis and imbalance.

concomitant neuromuscular retraining and physical therapy, which can enhance the effectiveness of BT and lead to a more favorable and lasting result [23–26].

Two commercial forms of BT, type A (BTX-A) and type B (BTX-B), are currently available, identical in action but differing in potency. BTX-A and BTX-B are also thought to also vary slightly in onset, duration and diffusion [4,27]. BTX-A and BTX-B are produced by different strains of Clostridium botulinum, with BTX-A being the most powerful and common form used clinically [1,28]. Other C. botulinum strains include C, D, E, F and G, none of which has yet been used to commercially produce BT [4,29,30]. The most universally available forms of BT are onabotulinumtoxinA (ONA; Botox Cosmetic and Vistabel, Allergan, Inc., Irvine, California) and abobotulinumtoxinA (ABO; Dysport, Medicis Aesthetics, Inc., Scottsdale, Arizona; Azulure, Galderma Laboratories, Lausanne, Switzerland), both types of BTX-A with differing manufacturing processes, resulting in different concentrations and nontoxic proteins. BTX-B is available as rimabotulinumtoxinB (Myobloc, Solstice Neurosciences, LLC, Louisville, Kentucky) but is yet to be well established in the treatment of facial muscular disorders, and is only FDA approved for cervical dystonia [4,31,32,33]. Theoretically all forms of BT can be used similarly in treatment, keeping in mind the differences in potency [12,34]. There are reports of decreased efficacy and increased tolerance of BTX-A, with response to BTX-B in these cases [14,16,35]. Given the general lifelong need for BT in facial paralysis, as well as the ever-increasing number of patients receiving this treatment, BTX-A tolerance could eventually be seen more frequently in this population.

For consistency, we refer to the ONA form of BTX-A (hereafter referred to as BT).

TEXT OF REVIEW

Facial musculature

In considering the application of BT to a patient suffering from acute or chronic facial paralysis, it is important to have an understanding of the facial musculature and its role in aesthetics and function (Fig. 1). As discussed below, depending on the individual patient dysfunction, various combinations of these muscles will require BT injection.

Synkinesis and hyperkinesis

Flaccid paralysis versus synkinesis

Individuals who suffer irreversible and complete facial nerve paralysis have very different functional and aesthetic outcome than those who have regeneration of the facial nerve or undergo cranial nerve substitution techniques such as hypoglossal–facial nerve transfer. Flaccid paralysis results in significant functional deficits such as oral incompetence, poor articulation, lip and buccal mucosa biting, as well as lagophthalmos with potential for corneal ulceration and blindness. Furthermore, these individuals develop an effaced nasolabial fold, severe facial atrophy, brow and facial ptosis and absent animation, most importantly smile mechanism, on the affected side.

Patients who undergo cranial nerve substitution techniques, direct or cable nerve grafting, or have reversible facial nerve palsy such as Bell’s palsy may develop synkinesis. Synkinesis is defined as the involuntary movement of one mimetic muscle group with the voluntary movement of a second muscle group. Classically, synkinesis is thought to arise from the aberrant regeneration of facial nerve fibers, but has also been theorized to result from ineffective myelination (leading to nerve cross-talk), or a centralized, postinjury hypersensitization of the facial nucleus [23,36]. Synkinesis occurs in up to 10% of patients after recovery from Bell’s palsy [27,37].

Synkinesis can also result in functional deficits similar to flaccid paralysis; the visible facial deformities, however, are quite different than in cases of
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complete paralysis. Patients typically have resting and dynamic facial asymmetry; hyperactivity of facial muscles; eyelid aperture narrowing; poor oral commissure excursion and smile mechanism; hyperlacrimation; deepening of the nasolabial fold; a prominent platysma and eyebrow elevation. Although the mechanism of action for smile dysfunction with synkinesis is controversial, the hyperkinetic activity of the platysma, buccinators and depressor anguli oris is likely a contributing factor to the limitation in oral commissure excursion.

Synkinetic movements are traditionally labeled with a composite term, whereby the muscle group of intended movement is followed by the muscle group of unintended movement; i.e., ‘oculo-oral’ involves the involuntary movement of the oral commissure with voluntary eye closure. Although synkinesis is best thought of as on a spectrum, oculo-oral and oro-ocular remain the most common general forms of synkinesis, with several specific subcategories within these classes [20,28]. In particular, Marin-Amat’s syndrome (eye closure upon jaw opening or lateral jaw movement) and pseudoptosis (ptosis without malfunction of the levator palpebrae superioris or Mueller’s muscle) are two of the more commonly reported subtypes of oro-ocular synkinesis [29,30,38]. Synkinetic firing of the platysma is also frequently encountered with facial movements of eye closure and/or smile, resulting in cosmetic, functional and sometimes painful contraction [24–26,31,32,33∗,39–43].

Gustatory hyperlacrimation, or crocodile tear syndrome (CTS), which involves unintentional unilateral lacrimation with food consumption, is also thought to be a synkinetic sequelae of facial paralysis. It is suspected that CTS results from the misdirection of regenerating gustatory fibers through the greater petrosal nerve [34,44,45,46∗∗]. Given the general heterogeneity of synkinetic movement, standardized measurement has always been controversial and challenging, with intraobserver reliability varying considerably. Although the House–Brackmann scale is the most widely utilized grading system in facial paresis and paralysis, other scales, such as the Sunnybrook Facial Grading System, are also well studied but more comprehensively addressed synkinesis [35,47]. The Sunnybrook Facial Grading System has also specifically been used to evaluate the effectiveness of BT in the treatment of synkinesis [20,36∗,47]. Standardized patient-reported surveys have also been simultaneously employed alongside observer scales to study synkinesis [17,37]. To guide individualized treatment, we recommend that practitioners maintain a grading system for synkinesis throughout the care continuum.

Hyperkinesis and facial imbalance

The nonparalyzed side can also be targeted to create symmetry with the paralyzed or paretic side. Although the term ‘synkinesis’ is used to describe involuntary movement of one mimetic muscle group with the voluntary movement of a second muscle group on the affected side, ‘hyperkinesis’ is broadly used to define the asymmetric static and dynamic hyperactivity of the normal side. As a result, selective neuromodulation of specific facial muscles on the unaffected side can help create more resting and dynamic symmetry in patients with complete paralysis or synkinesis. Although not observed in the senior author’s (B.A.) practice, it has also been suggested that BT application on the unaffected side can positively affect the long-term recovery and function of the paralyzed side [20,48].

Technique

In addressing the patient with incomplete recovery from facial paralysis, it is crucial to take a global view of the disorder. In total paralysis without reinnervation, BT is only useful on the nonparalyzed face to balance movement and treat hyperkinesis; however, in most cases of partial recovery, patients suffering from long-term sequelae of facial paralysis are best served by concomitant treatment of synkinesis on the affected side, and compensatory hyperkinesis on the unaffected side.

Timing

Except in cases of confirmed facial nerve transection without surgical reinnervation, most recommend applying BT treatment on the affected side only after the majority of reinnervation is achieved. The underlying rational is to avoid overtreatment, and to prevent the introduction of confounding factors into tracking the natural course of recovery. In the case of Bell’s palsy, recovery is thought to occur within 4–6 months [17,34,38,49–51]. For those with surgical treatment, recovery has been observed up to a year postoperatively. Although patients can get worsening hyperkinesis after full potential of recovery is achieved, early normal-side BT balancing injections can be utilized.

BT takes effect within 12–18 h, lasting 3–6 months and with maximal effect 4–7 days after injection. Most will notice decreasing efficacy at
approximately 1 month. It typically takes several sessions to develop an individualized dosing regimen.

**Pretreatment**

Prior to BT injection, a full history should be obtained, with particular attention to the time course of the disorder, as well as any contraindications to BT use (pregnancy, lactation, myasthenia gravis, peripheral motor neuropathies, active infections or previous adverse reaction). Photographic and/or videographic documentation, facial analysis and grading should be performed, and an injection plan should subsequently be developed. Counseling should be provided regarding the injection process, timeline of effectiveness, side-effects and potential risks, particularly when treating new patients. A consent form should be obtained at each visit.

The intended areas of injection can be pre-treated. In our practice, we do not use any anesthesia, and apply only an alcohol wipe before injection. Some practices utilize ice compresses to promote vascular constriction and anesthesia and/or lidocaine/prilocaine cream (EMLA; Astra Zeneca, Milan, Italy).

We dilute 100 units of Botox in 4.0 ml of 0.9% saline for a concentration of 2.5 U in 0.1 ml and use a 1 ml syringe with a 32-gauge needle for delivery.

**Dosing**

In the case of synkinesis, the goal of BT treatment is to reduce or eliminate the involuntary muscle action that is aberrantly triggered, achieved by targeted BT injection into this muscle area. Dosing and injection location are specific to each patient. A deep knowledge of facial musculature anatomy, along with careful evaluation of individual facial movement, is key to determining required injection areas.

The typical regions on the affected side include the following: orbicularis oculi to reduce narrowing of eyelid aperture; platysma to reduce banding and tightness in the neck; buccinator; mentalis to reduce chin dimpling and occasionally the frontalis and corrugator supercilli to reduce tension and relax the forehead. The platysma, buccinators and depressor anguli oris need to be aggressively injected to improve the smile mechanism albeit usually with limited success.

The unaffected side is also injected to create balance, improve hyperkinesis and create more symmetry at rest and with animation in patients with complete paralysis or synkinesis. The following areas are usually considered: levator labii alaeque nasi to reduce the visibility of the upper teeth; depressor labii inferioris to reduce the visibility of the lower teeth and orbicularis oris and frontalis to match the contralateral rhytids (Fig. 2). The dosing ranges and areas of injection are outlined in Table 1.

Titration is necessary to minimize the effect on intended function while maximizing treatment of unintended motion. We recommend injecting lower-than-normal amounts at the initial treatment session, with a 2-week follow-up for possible additional injections. This allows for careful titration and precise understanding of the patient’s BT requirements. After several sessions, a customized dosing regimen should develop.
Concomitant exercises (i.e. mirror feedback)

Physical therapy in the form of neuromuscular retraining has been well documented in the treatment of synkinesis [24–26,34,39–43]. Several studies have also demonstrated the synergistic effect of physical rehabilitation combined with BT injection in the synkinetic and asymmetric facial paralysis patient. In particular, initiation of neuromuscular retraining and mirror biofeedback after BT injection has been shown to enhance the effects of BT injection, with persistent improvement in synkinesis and imbalance after the pharmacologic effects of BT have long dissipated [17,44,45,46**].
OTHER USES

Acute facial paralysis
Depending on the type of injury suffered, facial nerve paralysis or paresis is likely to fully resolve without any long-term sequelae. The acute post-injury period, usually defined as 3 months, has recently been discussed as a potential treatment window for BT application, particularly in patients who do not qualify for medical or surgical intervention [34,47,51]. Some studies have shown that weakening the unaffected side contributes to strengthening and improved functionality of the affected side; in this context, it’s been suggested but not proven that acute-phase BT injections could play a positive role in long-term recovery [20,34,47,51]. Although we rarely employ BT in our own practice during the acute phase of facial paralysis, this is a topic of ongoing discussion and controversy. Technique and dosing for normal side BT injection in the acute phase and chronic phase are identical, with emphasis on titration and patient education.

Hyperlacrimation
A rare complaint in facial paralysis patients is the development of lacrimation with taste stimulation (CTS), likely caused by rerouting of the facial nerve’s visceromotor fibers to the lacrimal gland [17,34]. After injury these autonomic facial nerve fibers may redirect, through the greater superficial petrosal nerve, to the lacrimal gland. Another explanation is that rather than nerve regeneration/reinnervation, an abnormal synapse occurs at the site of injury causing crossover of impulse from one fiber to another (afferent/efferent) [17,34,48–51]. In both instances, this aberrant neurophenomenon results in ipsilateral tearing when the patient eats. As the

| Table 1. Botulinum toxin dosing ranges for synkinesis |
|-----------------|-----------------|
| **Muscle**      | **Dose range (units of BT)** |
| **Affected side** |                  |
| Corrugator Supercilii | 5–10             |
| Orbicularis Oculi    | 2.5–7.5          |
| Buccinators          | 10–20            |
| Depressor Anguli Oris| 2.5–10           |
| Mentalis            | 2.5–10           |
| Platysma             | 10–30            |
| **Unaffected side** |                  |
| Frontalis            | 5–10             |
| Orbicularis Oculi    | 7.5–10           |
| Levator Labii Alaque Nasi | 2.5–7.5     |
| Depressor Labii Inferioris | 2.5–5        |
blepharoptosis with normal levator palpebrae superioris muscle [34,55]. As with all inci-
deries of post-BT ptosis, treatment with alpacloni-
dine 0.5%, or other alpha-adrenergic agonist eye

drops, can ameliorate this complication [53,56].

There is controversy as to the BT injection tech-
nique for CTS and, as this is a relatively rare condition, consensus is absent. Some authors prefer a transcutaneous injection without direct visualization of the gland [17,30,50], whereas others describe a transconjunctival approach with direct gland visualization [17,19,34,51,54]. In the author’s prac-
tice (G.G.M.), transconjunctival injections are pre-
ferred, as we find that less BT is required for successful treatment. Review of the literature demon-
strates a similar preference, due not only to the decreased BT requirements, but also to lower ptosis
risk. These differences are likely because of a more direct injection of the gland with the transconjunc-
tival method [30,34,51].

For transcutaneous injection, patients are asked to look infero-medially with injection at the inferior por-
tion of the junction of the middle and lateral third of the superior orbital rim. For transconjunc-
tival injection, after topical anesthesia is applied to the eye, the upper lid is everted whereas pressure is applied at the lateral canthus to expose the palpebral lobe of the lacrimal gland [30,34]. Ten to 20 units of BT are typically injected, always starting with a lower dose in new patients, with subsequent upward titration as needed [16,17,34,49–51].

Before injection, measurement of margin reflex distance should be performed while asking the patient to contract the orbicularis oculi through the pursing of lips. Using the margin reflex distance, as well as subjective patient feedback, effective injection amounts can be developed and utilized over time [30,31,57,58].

Alternative treatments

Given its effectiveness, ease of use and minimal inva-
siveness, BT has become the standard of care in synkinesis and hyperkinesis treatment; however, selective neuroectomy is the most utilized alternative when BT injections have become ineffective or are poorly tolerated, or in cases in which a more lasting solution is preferred [16,57]. This procedure involves transection of facial nerve branches observed to be contributing to synkinetic mis-firing or muscle over-
action. First described in 1950 by Marino and Alur-
ralde [55,58], it was later modified by Dobie and Fisch in 1986 to include extirpation and ablation of contrib-
utory branches under general anesthesia [31,56,59,60]. It has since been described as an excel-
ent option for synkinetic and hyperkinetic move-
ment of the platysma [31,60], and most recently as an alternative to BT for oro-ocular synkinesis. In the study by Hohman et al. facial nerve branches were extirpated under general anesthesia, with selective ablation of the offending branch(es) once the patient is awake and able to replicate aberrant movement [16,61]. Although initially effective, recurrence of the muscular disorder, occasionally in a more severe form, has been anecdotaly reported [28,62].
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Selective myectomy or myotomy has also been utilized in treatment of synkinesis and hyperkinesis, variously reported for periorbital, periocular and platysmal treatment in both the affected and unaffected sides [14,31,57,58]. The procedure involves isolation and transection of the problematic muscle, frequently in combination with other therapies such as grafting, neurectomy and BT. Several approaches have been developed, including direct treatment of hyperkinetic nasalis [16,57], ablation of perioral muscles in patients with oro-ocular synkinesis [30,58] and the ablation of involuntary synkinetic platysma or levator on the affected side [31,53,59,60]. Although generally unpredictable over the long term, platysmectomy has been reported successful in suppressing unwanted platysmal contraction and may be a suitable alternative to BT [60,63].

In our practice, we are currently looking into the effectiveness of selective neurectomy and myotomy as an alternative for BT injections to platysma and buccinators muscles.

Cryotherapy and radiofrequency are well described in their cosmetic application to skin and muscle [30,34,61], and time will tell whether these treatments can be applied to postparalytic sequelae currently treated with BT.

Pitfalls

In addition to the more common risks of BT injection, such as bruising and edema, BT injection for facial paralysis is slightly higher risk than typical cosmetic or targeted uses, given the higher cumulative dosage, riskier areas of injection and need for long-term, repeated use. Before initiation of treatment, patients should be counseled as to the potential side-effects and complications of BT injections.

There is controversy in the literature regarding the diminishing effectiveness of BT due to the development of antibodies [53,62,64]. Loss of BTX-A effectiveness could necessitate transition to different BT strains (e.g., BTX-B) in patients who no longer satisfactorily respond to BTX-A [14,53], or eventually require other more invasive forms of targeted muscle suppression (discussed above) [5,16]. In our practice, facial paralysis patients typically receive BTX-A injections every 3–4 months, and we have observed only rare occasions of increased tolerance. In these cases, titration of dosing has restored adequate effectiveness.

BT overtreatment is a potential issue, given the large quantity of BT typically required in facial paralysis patients. Although overtreatment can cause cosmetic and expressional deficiencies, such as smile dysfunction or brow ptosis, the most worrisome complication is the elimination of function, causing oral incompetence, speech abnormalities and lagophthalmos.

Oral incompetence and/or speech abnormalities are rare complications resulting from overinjection of the oral musculature (typically depressor anguli oris, depressor labii inferioris or levator labii alaeque nasi), or misinjection of the orbicularis oris. In our experience, overinjection of targeted oral musculature can cause transient speech difficulty and, rarely, oral incompetence. These issues tend to subside as patients quickly adapt to a new muscular equilibrium. We have never encountered a patient with long-term oral incompetence from orbicularis oris injection. The incidence of overtreatment can be minimized by carefully titrating up from lower doses when injecting new patients.

Lagophthalmos is a relatively common side-effect of BT treatment for pseudoptosis, as injection directly targets the palpebral portion of the orbicularis muscle (as discussed above) [30]. More rarely, lagophthalmos can result from overinjection and/or spread of injection from the orbicularis oculi, in attempting to treat aperture narrowing. As in any case of lagophthalmos, treatment should focus on corneal protection with aggressive eye lubrication and taping with sleep, until the orbicularis oculi suppression diminishes and full closure is once again achieved. Again, careful BT dose titration, especially in cases of pseudoptosis, can minimize the incidence of lagophthalmos.

Blepheroptosis is a relatively frequent complication of BT injection to the upper-third of the face, resulting in temporary cosmetic and visual disturbances. Caused by unintentional BT diffusion to the levator palpebrae superioris muscle, it is also hypothesized to occur after injection of the frontalis ‘unmasks’ a hidden ptosis, which had previously been counterbalanced by subtle frontalis action [53]. A recent meta-analysis demonstrated a dose-dependent 2.5% overall incidence of blepheroptosis with cosmetic injection, with up to 21% dose-dependent incidence with diffuse upper face injection [63]. Blepheroptosis is particularly common in the treatment of eye specific facial paralysis sequelae, given the significant proximity of the levator palpebrae superioris to required injections [30,34]. Blepheroptosis manifests between 48 h to 1 week following treatment, and typically resolves within 2–6 weeks [53,64]. It can be treated with titrated alpha-adrenergic agonist eye drops, such as apraclonidine 0.5%, stimulating Mueller’s muscle to elevate the lid [53].

Cases of systemic weakness and toxicity have been described with BT, although this rare
complication has been limited to patients receiving large doses of BT for treatment of nonfacial muscle disorders (i.e. cerebral palsy and poststroke spasm) [5], or in those treated with unapproved BT in exponentially larger concentrations than intended [2,3,13]. Although never reported in facial injection of approved pharmacologic BT, given both the larger-than-typical doses of BT and the routine treatment of children, practitioners using BT for facial paralysis should be familiar with the signs and symptoms of BT toxicity. Symptoms include generalized limb weakness, fatigue and dysphasia, with florid botulism, paralysis and respiratory arrest only reported in cases of injection of unapproved BT formulation in unintentionally high concentrations [1,2,5,6,15,17–22]. Although controversy exists as to the method of absorption, as well as the existence of cumulative or weight-based toxicity of BT, case reports have demonstrated rare systemic symptoms in repeated local BT injections of as little as 7 units of BTX-A per kilogram or totals of 600 units per session, but with doses of over 30 units per kilogram or totals of over 1200 units per session safely and repeatedly given [5,7–11,24–26]. Although prudent to keep in mind total dosage, especially in young children, total BT dosing should remain well under any level of concern in the course of treating facial paralysis patients.

CONCLUSION

BT injection has become indispensable in treating facial paralysis and its long-term sequelae. With general synkinesis, facial imbalance and hyperkinesis, the careful and targeted application of BT injections is well tolerated and effective. BT can also be successfully applied in the treatment of the more uncommon sequelae of hyperlacrimation and pseudoptosis. When using BT, the practitioner should be well versed in the subtleties of facial musculature and the potential pitfalls of injection. In our practice, we employ neuromuscular retraining and BT injection and believe that they can have synergistic activity in improving the symptoms of facial palsy. Future research will dictate whether selective neurectomy, myectomy, cryotherapy or radiofrequency can provide similar success in treatment, with longer-term or permanent improvements.

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