TITLE: Botulinum Toxin in Facial Nerve Paralysis: A Systematic Review

PRESENTER: Luca Guarda Nardini

PRESENTER (INSTITUTION ONLY): Aulss2 Marca Trevigiana Ca'Foncello Hospital

AUTHORS (FIRST NAME INITIAL LAST NAME): L. Guarda Nardini[2], D. Manfredini[3], S. Conte[4], M. Val[1]

AUTHORS/INSTITUTIONS: M. Val, University of Siena, Siena, ITALY;
L. Guarda Nardini, Unit of Oral and Maxillofacial Surgery, Aulss2 Marca Trevigiana Ca'Foncello Hospital, Treviso, ITALY;
D. Manfredini, University of Siena, Marina di Carrara, ITALY;
S. Conte, Pain Therapy Unit, Aulss2 Marca Trevigiana Ca'Foncello Hospital, Treviso, ITALY;

Introduction

Facial nerve palsy represents a significant clinical challenge, profoundly affecting patients' physical function, psychological well-being, and quality of life. The condition manifests through various etiologies, with Bell's palsy being the most common idiopathic form affecting approximately 20-30 cases per 100,000 persons annually [1]. Facial nerve injury can result from infectious, traumatic, neoplastic, autoimmune, congenital, or idiopathic causes, each requiring individualized management approaches. While approximately 80% of patients with Bell's palsy experience spontaneous recovery, significant numbers do not fully recover, particularly those with complete or prolonged paralysis [2].

The consequences of facial paralysis extend beyond motor dysfunction. Patients experience profound psychological and social impairments including low self-esteem, social isolation, anxiety, and depression [3]. The unilateral facial paralysis creates aesthetic asymmetry that is difficult for patients to accept, leading to decreased quality of life and functional incompetence. Following the acute phase, sequelae such as synkinesis—involuntary simultaneous movements occurring with voluntary facial expression—compound these difficulties and often prove more problematic than the initial paralysis [4].

The therapeutic landscape for facial nerve palsy has evolved considerably. While early intervention with corticosteroids and antivirals forms the foundation of acute management, the chronic phase requires adjunctive treatments to address residual deficits and synkinesis [5]. Botulinum toxin infiltrations have emerged as a cornerstone therapy in the chronic management arsenal, offering a minimally invasive approach to address facial asymmetry and synkinesis. This literature review comprehensively evaluates the use of botulinum toxin injections for treating facial nerve palsy, examining its efficacy, safety profile, mechanisms of action, optimal injection techniques, and integration within multidisciplinary treatment paradigms.

Material and Methods

Study Selection and Search Strategy

This comprehensive literature review was conducted through systematic searches of academic databases including PubMed, MEDLINE, and ScienceDirect, utilizing multiple search queries encompassing: "botulinum toxin facial nerve palsy," "botulinum toxin Bell's palsy," "botulinum

toxin facial synkinesis," "facial nerve reconstruction," and "nonflaccid facial palsy management." The search encompassed publications from 1989 to 2026, capturing seminal works on botulinum toxin's therapeutic emergence through contemporary clinical evidence. Studies were included if they addressed the use of botulinum toxin for facial nerve palsy management, reported on efficacy or safety outcomes, or provided mechanistic insights into the toxin's therapeutic action at the neuromuscular junction.

Inclusion Criteria

Publications were selected based on the following criteria: (1) studies describing clinical applications of botulinum toxin for facial nerve paralysis or synkinesis; (2) research examining mechanism of action relevant to facial muscle denervation; (3) trials evaluating efficacy outcomes using validated facial grading scales (House-Brackmann, Stennert Index, Sunnybrook Facial Grading Scale, Facial Disability Index); (4) investigations of adverse events and safety profiles; (5) comparative studies examining botulinum toxin versus alternative treatments or placebo; and (6) multidisciplinary management approaches incorporating botulinum toxin. Both prospective and retrospective studies, randomized controlled trials, systematic reviews, and clinical practice guidelines were included to provide comprehensive evidence synthesis.

Exclusion Criteria

Studies were excluded if they focused exclusively on cosmetic applications without addressing pathologic facial asymmetry, addressed botulinum toxin use in unrelated conditions without relevance to facial nerve pathology, were published in languages other than English without available translation, or provided only brief mentions of botulinum toxin without substantive clinical or mechanistic discussion.

Data Extraction and Outcomes Assessed

Data extracted from included studies encompassed: (1) patient demographics and characteristics; (2) etiology of facial nerve palsy; (3) botulinum toxin formulations used (onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA); (4) dosing regimens and injection sites; (5) primary efficacy outcomes measured through facial grading scales and quality of life questionnaires; (6) synkinesis improvement metrics; (7) adverse event documentation; (8) duration of therapeutic effect; (9) long-term outcomes and follow-up periods; and (10) comparative effectiveness data. Primary outcome measures included improvement in facial symmetry at rest, voluntary movement symmetry, synkinesis reduction, and patient-reported quality of life scores using validated instruments such as the Facial Disability Index (FDI) and patient-reported outcome measures (PROMs).

Results

Epidemiology and Clinical Presentation

Facial nerve palsy constitutes one of the most common cranial nerve injuries encountered in clinical practice. In a comprehensive multidisciplinary study of 1,220 patients with facial palsy treated between 2007 and 2018, 58.4% were female with a median age of 50 years, and 42.8% presented with chronic palsy beyond the 12-18 month window [6]. The patient population required diverse treatment modalities based on palsy phase and characteristics. Patients with

acute facial palsy were treated for a median of 3.6 months in the center, while those with chronic palsy required extended management averaging 10.8 months.

Bell's paralysis represents the most common presentation, though facial nerve injury occurs in various contexts including traumatic injury, surgical complications (particularly following vestibular schwannoma resection or parotid surgery), tumor infiltration, Ramsay Hunt syndrome associated with varicella-zoster virus reactivation, and Lyme disease. Post-paralytic synkinesis develops in approximately 10% of patients following facial nerve injury, representing a severe sequela characterized by involuntary facial movements accompanying voluntary expression [2]. The aberrant regeneration underlying synkinesis involves misrouting of regenerating nerve fibers such that a single motor neuron establishes connections with multiple target muscles, producing involuntary simultaneous contractions.

Mechanism of Action of Botulinum Toxin

Botulinum toxins represent among the most potent neurotoxins known, with efficacy at doses measured in nanograms [7]. The therapeutic mechanism involves highly selective blockade of acetylcholine release at the neuromuscular junction. The toxin's heavy chain (HC) contains a binding domain that recognizes cell surface receptors on motor nerve terminals, facilitating cellular uptake [8]. The light chain (LC), possessing zinc-dependent endopeptidase activity, subsequently cleaves SNARE (Soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptor) proteins essential for synaptic vesicle exocytosis.

Botulinum toxin type A (BoNT-A) specifically cleaves synaptosomal-associated protein 25 (SNAP-25), preventing acetylcholine-containing vesicle fusion with the presynaptic membrane [9]. This results in blockade of neurotransmitter release with consequent muscle denervation and paralysis. The paralytic effect is reversible and temporary, typically lasting 12-16 weeks before regeneration of acetylcholine receptors and restoration of neuromuscular transmission occurs.

Recent research has revealed that botulinum toxin effects extend beyond the peripheral neuromuscular junction. Studies using primary neurons and microfluidic systems demonstrate that BoNT-A undergoes retrograde axonal transport following injection into muscle, traveling to the soma via fast axonal transport mechanisms [10]. Furthermore, catalytically active BoNT-A is transported to second-order neurons through transcytosis, with selective uptake into cholinergic synapses within the central nervous system. This retrograde action on central cholinergic circuits may contribute to therapeutic benefits beyond peripheral paralysis, particularly relevant to synkinesis management where central compensatory mechanisms participate in symptom generation.

The toxin's action involves activity-dependent uptake into synaptic vesicles followed by transport within autophagosome carriers to the soma [11]. Blocking autophagosome formation or acidification inhibits central trafficking, demonstrating that presynaptic activity regulates BoNT-A uptake and retrograde transport. These mechanisms suggest the clinical efficacy may involve both peripheral denervation of hyperactive muscles and modulation of central facial motor circuits contributing to facial asymmetry and synkinesis.

Clinical Applications in Facial Nerve Palsy

1. Bell's Palsy and Acute Facial Paralysis

Bell's palsy, characterized by acute unilateral facial paralysis with unknown etiology, traditionally receives early intervention with corticosteroids and antivirals. In the acute phase, botulinum toxin plays a limited role, with primary management focused on preventing further progression and supporting recovery. However, among patients with incomplete recovery or severe paralysis at presentation, botulinum toxin becomes relevant for management of residual asymmetry and synkinesis in subsequent phases.

A comprehensive analysis of 42,866 patients with facial paralysis identified from claims databases revealed that steroids were provided to 50.1-59.8% of adults, antivirals to 26.2-39.4%, while botulinum toxin injections were administered to only 0.1-0.8% within the first 2 years post-diagnosis [12]. This suggests significant underutilization of botulinum toxin despite evidence for efficacy. The delay in implementing chemodenervation therapy may reflect limited awareness or access rather than lack of clinical benefit.

2. Facial Synkinesis Management

Post-paralytic facial synkinesis represents one of the most challenging and distressing sequelae of facial nerve injury. The International Head and Neck Scientific Group conducted a systematic review of 132 articles published from 2008 onward to establish evidence-based recommendations for facial synkinesis management [4]. The consensus established that facial training based on biofeedback retraining constitutes first-line treatment, with botulinum toxin representing second-line therapy for patients with inadequate response to physical rehabilitation. Surgery, including selective neurectomy and myectomy, is reserved for individual cases with unsatisfactory response to conservative measures.

A landmark study evaluating botulinum toxin type A injection for facial synkinesis demonstrated the treatment's effectiveness in reducing synkinesis and improving facial expression symmetry, both at rest and during voluntary movements [13]. The mechanism involves selective paralysis of muscles displaying synkinetic hyperactivity on the affected side, reducing unwanted involuntary contractions that accompany voluntary facial movements.

3. Treatment Following Neurosurgical Interventions

Facial nerve injury represents a significant complication of neurosurgical procedures, particularly following vestibular schwannoma resection via translabyrinthine or transcochlear approaches. IncobotulinumtoxinA treatment of post-neurosurgery facial nerve palsy demonstrated significant improvements in facial symmetry in patients with facial nerve injury following neurosurgical interventions [14]. Patients receiving incobotulinumtoxinA injections showed significant improvements on House-Brackmann, Yanagihara System, and Sunnybrook Facial Grading scales after 1 month of treatment, compared with 3 months required for standard rehabilitation in control groups.

A long-term follow-up study of 86 patients with facial neuropathy after posterior cranial fossa and cerebellopontine angle tumor surgery found that BTA treatment initiated early after facial

nerve injury produced significantly superior outcomes compared to rehabilitation alone, assessed using the Sunnybrook Facial Grading Scale and Facial Disability Index over 5 years [15]. Resting symmetry, voluntary movement symmetry, and synkinesis were significantly better in the BTA group at 1, 2, 3, and 5 years post-surgery. Crucially, no need for dose adjustment was observed over the 5-year period, suggesting sustained efficacy without development of resistance. Physical and social functioning scores on the Facial Disability Index were significantly elevated in the BTA group, indicating substantial quality of life improvements.

Efficacy Data from Clinical Studies

Facial Symmetry and Motor Function Outcomes

A multidisciplinary facial nerve center treatment analysis demonstrated that botulinum toxin injections dominated the chronic treatment phase, with 11% of 1,220 patients receiving BoNT-A treatment [6]. These patients showed highly significant improvements according to facial grading scales (Stennert index), the Facial Disability Index (FDI), and the Facial Clinimetric Evaluation (FaCE) scale, with statistical significance at $p < 0.001$. Motor function improvements were significant at $p < 0.001$, and facial-specific quality of life measures (FDI, FaCE) showed improvements at $p < 0.05$.

Hemifacial Spasm Treatment

Hemifacial spasm, characterized by involuntary unilateral facial muscle contractions, represents another significant indication for botulinum toxin therapy. A comprehensive review of 23 published studies between 1991 and 2021 evaluating botulinum toxin effectiveness and safety in hemifacial spasm treatment revealed efficacy rates ranging from 73% to 98.4%, with mean duration of therapeutic effect approximately 12 weeks [16]. Notably, effectiveness did not decrease over time with repeated injections in most studies examined. Adverse effects were uniformly mild and transient, with no serious complications reported in the reviewed literature.

The efficacy and tolerability of different botulinum toxin preparations (onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA) appeared similar in comparative studies. However, among studies, considerable variability existed in dosage used, muscles injected, intervals between treatments, and rating scales employed, creating challenges in direct comparison between studies.

Long-Term Efficacy and Quality of Life

Quality of life improvements represent critical outcome measures in facial nerve palsy management. A study analyzing quality of life in hemifacial spasm patients before and after microvascular decompression (MVD) or botulinum toxin therapy found that both treatments significantly improved quality of life indicators measured by the HFS-7 scale [17]. Patients with milder disease and better baseline quality of life showed preference for botulinum toxin therapy, while those with more severe disease progression more frequently selected surgical intervention.

Mechanism-Based Efficacy for Synkinesis

The theoretical basis for botulinum toxin efficacy in post-paralytic synkinesis involves selective weakening of muscles on the affected side displaying hyperactivity. By reducing the muscle

force of synkinetic muscles during voluntary movement, the treatment diminishes the proportion of movement that appears involuntary or uncontrolled. Additionally, retrograde transport and central effects may contribute by modulating facial motor cortex activity and reducing hyperexcitability of facial nucleus motoneurons secondary to aberrant regeneration.

Motor control deficits in facial synkinesis patients demonstrate neuroimaging evidence of cerebral cortex involvement, with increased amplitude of low-frequency fluctuations in sensorimotor areas [18]. Botulinum toxin may influence these cortical changes through central mechanisms, potentially explaining effects lasting longer than peripheral acetylcholine receptor regeneration.

Injection Technique and Dosing

Standard Injection Sites and Dosing

Botulinum toxin type A to improve facial symmetry requires precise anatomical knowledge and careful dose titration [3]. For facial palsy management, injections target specific muscles based on clinical examination findings. On the paretic (weak) side, injections focus on muscles with severe paralysis to minimize further denervation. On the contralateral (normal) side, injections target muscles displaying compensatory hyperactivity attempting to achieve midline symmetry.

Common injection sites include the orbicularis oculi for periocular synkinesis, zygomaticus major and minor for smile asymmetry, levator labii superioris for upper lip asymmetry, and depressor anguli oris for lower lip and chin asymmetry. Total dosing varies based on formulation: onabotulinumtoxinA typically ranges from 20-60 units per muscle group, abobotulinumtoxinA from 50-150 units (at a 3:1 potency ratio), and incobotulinumtoxinA from 16-40 units.

The correct injection technique is paramount, as over-injection results in lack of function leading to a paralyzed appearance and functional incompetence, potentially causing greater patient distress than the original asymmetry [3]. Therefore, the objective is achieving optimal dosage that improves symmetry without creating new functional deficits.

Localization Techniques

Over 25 years of pediatric botulinum toxin treatment experience has refined localization techniques, with evolution from palpation-guided injections to electromyography-guided and ultrasound-guided approaches [19]. Electromyography guidance helps identify motor endplate locations for maximal efficacy. Ultrasound-guided injection significantly improves accuracy of botulinum toxin delivery, particularly for salivary gland injections and deep facial muscles. For accurate botulinum toxin injection, identifying intramuscular neural distribution and motor endplate locations using modified Sihler techniques has identified optimal injection zones between specific anatomical landmarks.

Formulation-Specific Considerations

Three botulinum toxin type A formulations are currently available clinically: onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin). These products differ in manufacturing processes, excipient content, and potency units [20]. Mean light chain content per vial was measured as 2.69 ng/500 U for Dysport, 0.90 ng/100 U for Botox, and 0.40

ng/100 U for Xeomin, with clinically relevant differences at FDA-approved doses for upper limb spasticity. These neurotoxin content differences may influence duration of action reported across formulations.

Clinical comparison studies have shown earlier onset and longer duration of effect in higher percentages of individuals with abobotulinumtoxinA compared to onabotulinumtoxinA in treating facial lines [21]. IncobotulinumtoxinA provides an alternative formulation particularly useful in patients developing antibodies to onabotulinumtoxinA, though switching to alternative formulations can restore efficacy in approximately 80-90% of antibody-positive patients.

Safety Profile and Adverse Events

General Safety Considerations

Botulinum toxin represents a remarkably safe therapeutic agent when used at appropriate doses with proper injection technique. A comprehensive review of botulinum toxin therapy indicated that transient and benign adverse events predominate over serious complications, with systemic spread of toxin leading to botulism representing the most severe but extremely rare event [22]. Benign side effects are well-localized, reversible, self-limited complications developing within days of injection and typically resolving without treatment.

Common Adverse Events

The most frequent adverse events following facial botulinum toxin injection include localized pain or hematoma at injection sites, generally resolving within days. Facial-specific adverse effects include ptosis of the eyelid or eyebrow, eyebrow asymmetry, diplopia, lagophthalmos (inability to close eye completely), palpebral ectropion, and prominence of palpebral bags [23]. These complications can be minimized through knowledge of regional anatomy, adequate individualized planning based on frontalis muscle patterns, and identification of safety zones. When safety zones are respected, the incidence of complications approaches nearly zero.

In a questionnaire-based study of adverse events in cerebral palsy patients receiving botulinum toxin type A, adverse events or side effects occurred in 51% of treatments performed [24]. Of 95 adverse events and side effects reported, 50 were generalized and/or focal distant effects. However, severe adverse events requiring treatment discontinuation occurred in only 4% of cases. Temporary focal weakness of adjacent muscles and injection site pain represented the predominant complaints.

Immunogenicity and Antibody Development

A significant long-term consideration involves development of neutralizing antibodies against botulinum toxin, reducing therapeutic response. The phenomenon has been termed "resistance" or "secondary non-responsiveness" and occurs in approximately 10-15% of patients receiving repeated injections [2]. Development of antibodies appears related to cumulative dose exposure and injection frequency. Patients developing antibodies often experience complete loss of therapeutic effect despite dose escalation.

The strategy for managing antibody development involves switching to alternative botulinum toxin formulations or serotypes. Botulinum toxin type B (rimabotulinumtoxinB) represents an

alternative when type A antibodies develop, though patients may develop antibodies to type B over time. In a series of 390 patients treated with botulinum toxin, only 10 (2.6%) required switching to type B, indicating this complication remains relatively uncommon.

Serious Adverse Events

Though rare, systemic spread of botulinum toxin beyond the injection site can cause botulism characterized by flaccid descending paralysis beginning with cranial nerve palsies and potentially progressing to extremity weakness and respiratory failure [25]. Preventive measures include using appropriate doses, proper injection technique, and careful patient selection, with avoidance in patients with neuromuscular junction disorders such as myasthenia gravis or Lambert-Eaton syndrome.

An outbreak of iatrogenic botulism resulted from injection of counterfeit BoNT-A preparation in Egypt in 2017 [26]. Nine patients developed severe botulism with doses of 200-300 IU, substantially higher than therapeutic facial doses of 20-60 IU per muscle. Patients presented with bilateral ptosis, diminished gag reflex, ophthalmoparesis, facial paresis, and tongue weakness. Early administration of trivalent A/B/E antitoxin provided rapid symptom reversal. This outbreak emphasizes the critical importance of obtaining botulinum toxin exclusively from licensed pharmaceutical sources ensuring product safety and authenticity.

Comparative Effectiveness with Other Treatments

Multidisciplinary Management Approach

Facial nerve palsy management optimally occurs through multidisciplinary coordination including otolaryngologists, neurologists, plastic surgeons, physiatrists, physical therapists, and speech-language pathologists. The standardized multidisciplinary team approach in a facial nerve center led to improved facial and emotional function in patients with acute or chronic facial palsy [6]. In the acute phase, corticosteroids and acyclovir dominated treatment (47.2% of acute palsy patients), followed by significant improvement of all outcome measures.

In the chronic phase, EMG biofeedback training (21.3%) and botulinum toxin injections (11%) dominated treatment, both leading to highly significant improvements. Upper eyelid weight placement (3.8%) and hypoglossal-facial-nerve jump suture (2.5%) represented surgical methods producing additional improvement. This multidisciplinary approach recognition that no single modality addresses all sequelae of facial paralysis.

Facial Training and Physical Rehabilitation

Physical rehabilitation through facial exercise therapy represents the first-line treatment for post-paralytic facial synkinesis. A systematic review of facial exercise therapy effectiveness identified seven high-quality randomized controlled trials, nine observational studies, and three quasi-experimental studies involving 854 participants [27]. Seventy-five percent of studies utilized validated measures to record changes in facial function or patient-rated outcomes. High-quality trials (4/7) all reported positive impacts of therapy, as did observational studies rated as high or moderate quality (3/9).

The benefit of facial exercise therapy varied with time points post-onset and clinical severity. Early intervention appeared more effective, though newer research strengthened evidence for value in chronic cases beyond one year post-injury. However, standardization differences across studies prevented meta-analysis to strengthen estimates of therapy effects.

Selective Neurectomy

For patients with refractory periocular synkinesis unresponsive to botulinum toxin and physical rehabilitation, two-step highly selective neurectomy offers refined surgical management [2]. Three patients aged 35-50 years underwent this procedure after failed botulinum toxin treatment. The two-step approach involved facial dissection under general anesthesia to identify specific nerve branches innervating periocular muscles, followed by selective neurectomy performed under local anesthesia with patient feedback to achieve exact degree of orbicularis oculi weakening required to decrease ocular irritation while avoiding lagophthalmos. All three patients experienced substantial improvement in palpebral fissure measurements at postoperative evaluation, with no development of lagophthalmos, xerophthalmia, or ectropion.

Comparison with Surgical Decompression

For patients with complete facial paralysis, debate continues regarding early surgical decompression benefit. A meta-analysis comparing middle fossa decompression (MFD), transmastoid decompression (TMD), and medical controls found MFD performed within 14 days of symptom onset produced average House-Brackmann scores of 1.8, superior to MFD after 14 days (2.75) and compared to medical controls (2.4) [28]. However, TMD did not offer improved outcomes over medical controls (HB 2.3 versus 2.4). This analysis suggests limited benefit from surgical decompression, supporting medical management as standard approach with selective surgical intervention reserved for specific scenarios.

Discussion

Efficacy Summary and Clinical Evidence

The evidence base supporting botulinum toxin use for facial nerve palsy management has expanded substantially since the toxin's initial therapeutic application in 1989. Current evidence demonstrates consistent and reproducible efficacy across multiple clinical contexts including Bell's palsy, post-traumatic facial paralysis, post-neurosurgical facial nerve injury, hemifacial spasm, and post-paralytic synkinesis.

In a multidisciplinary treatment series of 1,220 patients, botulinum toxin injections in the chronic phase led to highly significant improvements according to multiple validated facial grading and quality of life scales ($p < 0.001$ for motor function, $p < 0.05$ for quality of life measures). Long-term follow-up data extending to 5 years demonstrates sustained efficacy without loss of effect or need for dose escalation, contrary to theoretical concerns about progressive resistance [15]. These findings establish botulinum toxin as a durable, reliable adjunctive treatment for chronic facial paralysis.

For hemifacial spasm specifically, efficacy rates ranging from 73% to 98.4% with mean duration of 12 weeks represent remarkably consistent therapeutic responses [16]. The consistency of efficacy across different patient populations, disease durations, and clinical settings suggests

robust therapeutic benefit that does not substantially diminish with time or repeated treatments in most patients.

Mechanistic Insights and Central Effects

Traditional understanding of botulinum toxin mechanism limited the action to peripheral neuromuscular junction blockade. However, emerging research reveals more complex mechanisms contributing to clinical efficacy. Retrograde axonal transport, transcytosis into second-order neurons, and central modulation of facial motor circuits appear to contribute to therapeutic benefits, particularly in post-paralytic synkinesis management.

The demonstration that BoNT-A undergoes retrograde transport to the facial nucleus and cleaves SNAP-25 in central cholinergic synapses has important implications [10]. Post-paralytic synkinesis involves aberrant reinnervation with misrouting of regenerating motor nerve axons establishing inappropriate connections with facial muscles. Central motor control mechanisms compensate through increased drive to intact facial muscle motor pools. Botulinum toxin targeting central facial motor circuits may reduce this maladaptive central plasticity, providing benefit beyond peripheral denervation.

Motor control deficits in facial synkinesis patients show abnormal sensorimotor cortex activation with increased low-frequency fluctuations [18]. These findings suggest centrally mediated mechanisms involving the facial motor cortex and facial nucleus contribute to synkinesis generation. Botulinum toxin modulation of central cholinergic neurotransmission may normalize these pathologically altered neural circuits, contributing to long-term synkinesis improvement.

Optimal Patient Selection and Treatment Timing

While botulinum toxin demonstrates efficacy across facial paralysis types, optimal patient selection and treatment timing require clinical judgment. In acute Bell's palsy, early intervention focuses on corticosteroids and antivirals, with botulinum toxin reserved for patients developing residual asymmetry or synkinesis after initial recovery plateau. For post-neurosurgical facial paralysis, earlier botulinum toxin administration (within months of injury) appears beneficial based on evidence that incobotulinumtoxinA provided superior outcomes versus delayed rehabilitation in early and chronic phases.

The International Head and Neck Scientific Group consensus identifies facial training through biofeedback retraining as first-line treatment for post-paralytic synkinesis, followed by botulinum toxin for inadequate response [4]. This staged approach reflects evidence that physical rehabilitation provides durable benefits without medication effects, while botulinum toxin offers supplementary benefit in refractory cases. However, patients with severe synkinesis or significant functional impairment may benefit from earlier botulinum toxin introduction in combination with physical rehabilitation.

Integration Within Multidisciplinary Care Frameworks

Contemporary management of facial nerve palsy increasingly emphasizes multidisciplinary coordination. The standardized approach at comprehensive facial nerve centers, incorporating otolaryngologists, neurologists, plastic surgeons, physiatrists, and therapists, produces superior

outcomes compared to isolated specialty management [6]. Botulinum toxin injections represent one component within comprehensive treatment frameworks addressing multiple sequelae of facial paralysis.

Adequate patient assessment before botulinum toxin administration includes facial grading using validated instruments (House-Brackmann, Stennert index, Sunnybrook Facial Grading Scale), characterization of specific facial asymmetries and synkinesis patterns, assessment of tear production and ocular surface health, and comprehensive quality of life evaluation. This detailed assessment informs individualized injection planning, optimal dosage selection, and targeted muscle selection.

Safety Considerations and Risk Mitigation

Botulinum toxin demonstrates an excellent safety profile when administered by experienced practitioners using proper injection technique. The most frequent adverse events—injection site pain and temporary local muscle weakness—resolve spontaneously within days to weeks. Complication rates approaching zero when safety zones are respected emphasize the importance of anatomical knowledge and careful injection site selection.

The risk of antibody development leading to secondary non-responsiveness remains relatively low (10-15% of patients with repeated injections) and addressable through switching to alternative formulations or serotypes. Serious systemic complications including botulism occur only with inappropriate doses or contaminated products, emphasizing the critical importance of obtaining botulinum toxin exclusively from licensed pharmaceutical manufacturers.

Patients with underlying neuromuscular junction disorders, pregnant women, and those taking aminoglycosides require careful consideration or avoidance of botulinum toxin therapy due to potential for potentiated neuromuscular blockade. Careful history and physical examination before treatment initiation identifies these at-risk populations.

Limitations of Current Evidence and Future Directions

Despite substantial evidence supporting botulinum toxin efficacy, several limitations warrant acknowledgment. Most published studies employ relatively small patient samples with variable methodologies, injection techniques, dosing regimens, and outcome assessment tools. The heterogeneity prevents robust meta-analyses and direct comparisons between studies. Randomized controlled trials directly comparing botulinum toxin to placebo, physical rehabilitation, or other interventions in facial nerve palsy remain limited, though observational data consistently demonstrate efficacy.

Long-term data extending beyond 2-3 years remain sparse, though emerging 5-year follow-up data demonstrate sustained efficacy. The cost of botulinum toxin therapy and variability in insurance coverage create barriers to access, potentially contributing to underutilization observed in large claims database analyses where only 0.1-0.8% of facial paralysis patients received botulinum toxin treatment.

Future research should address: (1) optimal timing of botulinum toxin introduction relative to injury onset and baseline facial function; (2) comparative effectiveness studies versus physical

rehabilitation alone or combination approaches; (3) factors influencing individual response variability and antibody development; (4) central mechanisms of action and cortical plasticity changes associated with treatment; (5) long-term outcomes beyond 5 years; and (6) cost-effectiveness analyses supporting healthcare system utilization and reimbursement policies.

Conclusion

Botulinum toxin infiltrations represent an evidence-supported, effective, and safe adjunctive treatment for facial nerve palsy sequelae, particularly post-paralytic synkinesis and persistent facial asymmetry. The substantial body of evidence demonstrates consistent improvements in facial symmetry, facial function, and quality of life across multiple facial paralysis etiologies, clinical settings, and patient populations. Long-term follow-up studies extending to 5 years confirm sustained efficacy without progressive loss of effect.

The therapeutic mechanism involves not only peripheral neuromuscular junction blockade but also increasingly recognized central effects through retrograde transport and modulation of facial motor circuits. Optimal efficacy occurs within multidisciplinary management frameworks incorporating physical rehabilitation, surgical interventions when appropriate, and supportive care addressing functional deficits and psychological consequences of facial paralysis.

Botulinum toxin administration requires detailed anatomical knowledge, careful patient selection, precise injection technique, and individualized dose titration to achieve favorable outcomes while minimizing complications. The safety profile is excellent when administered by experienced practitioners using proper technique and appropriate patient selection. Current evidence establishes botulinum toxin as the treatment of choice for post-paralytic facial synkinesis unresponsive to physical rehabilitation, with established benefit for persistent facial asymmetry in chronic facial paralysis from any etiology.

Future clinical practice should emphasize earlier integration of botulinum toxin within comprehensive multidisciplinary management protocols, particularly for patients following neurosurgical procedures affecting the facial nerve. Standardization of injection protocols, outcome measurement instruments, and investigation of central mechanisms of action should receive priority to optimize therapeutic benefit and advance understanding of botulinum toxin's evolving role in facial nerve paralysis management. The existing evidence base, combined with the toxin's favorable risk-benefit profile and consistent efficacy, supports continued clinical utilization and further research to refine optimal treatment algorithms in this challenging patient population.

References

[1] P. N. de Lima, R. M. Gusmo, N. C. G. Siqueira, and L. C. Varejo, “TOXINA BOTULNICA COMO ALTERNATIVA NO TRATAMENTO DA PARALISIA FACIAL DE BELL: REVISO DE LITERATURA/ BOTULINUM TOXIN AS AN ALTERNATIVE IN THE TREATMENT OF BELL FACIAL PALSY: LITERATURE REVIEW,” *Brazilian Journal of Development*, 2020.

[2] M. H. Hohman, L. N. Lee, and T. A. Hadlock, “Twostep highly selective neurectomy for refractory periocular synkinesis,” *Wiley*, 2013.

[3] C. de Sanctis Pecora and D. Shitara, “Botulinum toxin type a to improve facial symmetry in facial palsy: A practical guideline and clinical experience,” *Toxins*, 2021.

[4] G.-L. O *et al.*, “Pathogenesis, diagnosis and therapy of facial synkinesis: A systematic review and clinical practice recommendations by the international head and neck scientific group.” 2022.

[5] H. Shawly *et al.*, “Surgical treatment of acute and chronic facial paralysis,” *Journal of Healthcare Sciences*, 2023.

[6] J. Steinhuser *et al.*, “Multidisciplinary care of patients with facial palsy: Treatment of 1220 patients in a german facial nerve center,” *Journal of Clinical Medicine*, 2022.

[7] N. Ayoub, “Botulinum toxin therapy: A comprehensive review on clinical and pharmacological insights,” *Journal of Clinical Medicine*, 2025.

[8] M. Y. Park and K. Y. Ahn, “Scientific review of the aesthetic uses of botulinum toxin type a,” *None*, 2021.

[9] D. Poenaru, M. Sndulescu, and D. Cintez, “Pain modulation in chronic musculoskeletal disorders: Botulinum toxin, a descriptive analysis,” *Biomedicines*, 2023.

[10] M. Caleo *et al.*, “Transynaptic action of botulinum neurotoxin type a at central cholinergic boutons,” *Society for Neuroscience*, 2018.

[11] T. Wang *et al.*, “Control of autophagosome axonal retrograde flux by presynaptic activity unveiled using botulinum neurotoxin type a,” *Society for Neuroscience*, 2015.

[12] T. Shokri, R. Saadi, lise Schaefer, and J. G. Lighthall, “Trends in the treatment of bell”s palsy,” *Thieme Medical Publishers (Germany)*, 2020.

[13] E. D. Toffola, F. Furini, C. Redaelli, E. Prestifilippo, and M. Bejor, “Evaluation and treatment of synkinesis with botulinum toxin following facial nerve palsy,” *Informa*, 2010.

[14] M. Akulov *et al.*, “IncobotulinumtoxinA treatment of facial nerve palsy after neurosurgery.” *Journal of Neurological Sciences*, 2017.

[15] M. Akulov, O. Orlova, V. Shimansky, S. Tanyashin, V. Poshataev, and V. Zakharov, “[Five-year follow-up after neurosurgery complicated by facial neuropathy].” *Voprosy neirokhirurgii imeni N N Burdenko*, 2024.

[16] N. Tambasco, M. Filidei, P. Nigro, L. Parnetti, and S. Simoni, “Botulinum toxin for the treatment of hemifacial spasm: An update on clinical studies,” *Toxins*, 2021.

[17] A. Trashin, Y. Shulev, and E. M. Bogdanova, “[Quality of life in patients with hemifacial spasm after microvascular decompression and botulinum toxin therapy].” *Voprosy neirokhirurgii imeni N N Burdenko*, 2023.

[18] J. Wu *et al.*, “Motor control deficits in facial synkinesis patients: Neuroimaging evidences of cerebral cortex involvement,” *Hindawi Publishing Corporation*, 2019.

[19] H. Stil, “Over 25 years of pediatric botulinum toxin treatments: What have we learned from injection techniques, doses, dilutions, and recovery of repeated injections?” *Toxins*, 2020.

[20] M. Field *et al.*, “AbobotulinumtoxinA (dysport), OnabotulinumtoxinA (botox), and IncobotulinumtoxinA (xeomin) neurotoxin content and potential implications for duration of response in patients,” *Multidisciplinary Digital Publishing Institute*, 2018.

[21] R. Kassir, A. Kolluru, and M. Kassir, “Triple-blind, prospective, internally controlled comparative study between AbobotulinumtoxinA and OnabotulinumtoxinA for the treatment of facial rhytids,” *Adis, Springer Healthcare*, 2013.

[22] H. Witmanowski and K. Bochowiak, “The whole truth about botulinum toxin a review,” *Advances in Dermatology and Allergology*, 2019.

[23] A. Borba, S. Matayoshi, and M. Rodrigues, “Avoiding complications on the upper face treatment with botulinum toxin: A practical guide,” *Aesthetic Plastic Surgery*, 2021.

[24] I. Baszczyk, N. P. Foumani, C. Ljungberg, and M. Wiberg, “Questionnaire about the adverse events and side effects following botulinum toxin a treatment in patients with cerebral palsy,” *Toxins*, 2015.

[25] A. K. Rao, J. Sobel, K. ChathamStephens, and C. Lquez, “Clinical guidelines for diagnosis and treatment of botulism, 2021,” *None*, 2021.

[26] E. A. M. A. Rashid, N. M. El-Mahdy, H. S. Kharoub, A. S. Gouda, N. A. El-Nabarawy, and B. Mgarbane, “Iatrogenic botulism outbreak in egypt due to a counterfeit botulinum toxin a preparation a descriptive series of patient features and outcome,” *Wiley*, 2018.

[27] K. AJ *et al.*, “Physical therapy for facial nerve paralysis (bell”s palsy): An updated and extended systematic review of the evidence for facial exercise therapy.” 2022.

[28] G. C. Casazza, S. Schwartz, and R. Gurgel, “Systematic review of facial nerve outcomes after middle fossa decompression and transmastoid decompression for bell”s palsy with complete facial paralysis.” *Otology and Neurotology*, 2018.