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REVIEW ARTICLE

Alternative Clinical Indications of Botulinum Toxin

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Abstract
Botulinum toxin type A (BoNTA) is a powerful neurotoxin that inhibits acetylcholine release from presynaptic vesicles. The potency and safety profile of BoNTA grant the toxin vast therapeutic potential. It has been used off-label for a variety of dermatologic conditions. This review aims to analyze published literature regarding the benefits and risks of the off-label use of BoNTA beyond facial lines, including eccrine hidrocystomas, enlarged pores, keloids and hypertrophic scars, hidradenitis suppurativa, hyperhidrosis, masseter muscle hypertrophy, and salivary gland hypertrophy, among others. A MEDLINE search from January 2000 to December 2019 was conducted on the off-label uses of botulinum toxin in dermatology.

Key Points

Botulinum toxin type A is a well-tolerated, effective, and long-lasting therapeutic tool for off-label use in dermatology.

Botulinum toxin type A can be used for sweat reduction, pain/pruritus reduction, cosmetic enhancement, and hair growth.

Botulinum toxin type A plays a role as a first-line or adjuvant treatment for various dermatologic conditions.

1 Introduction

Botulinum toxin is a powerful neurotoxin produced by the gram-positive bacterium *Clostridium botulinum*. Seven serotypes of botulinum toxin (A, B, C1, D, E, F, G) have been identified. Both A and B serotypes are commercially available, but botulinum toxin type A (BoNTA) is most widely used. BoNTA is commercially available in the USA in four products: onabotulinumtoxin A (ona-BoNTA; Botox®), abobotulinumtoxin A (abo-BoNTA; Dysport®), incobotulinumtoxin A (inco-BoNTA; Xeomin®), and prabotulinumtoxin A (pra-BoNTA; Jeaveau®).

BoNTA inhibits the release of acetylcholine and other neurotransmitters from presynaptic vesicles. This chemoprevention of cholinergic neurons induces temporary muscle paralysis. BoNTA has been indicated for the reduction of local perspiration, pruritus, and vasodilation by inhibiting release of calcitonin gene-related peptide (CGRP) and substance P (SP). Recent findings suggest BoNTA directly inhibits mast cell degranulation, thereby reducing skin inflammation [1]. BoNTA injections can block cholinergic stimuli to localized apocrine, eccrine, and apocrine glands. It has been hypothesized that, by reducing perspiration in targeted areas, BoNTA could alleviate symptoms of several dermatologic diseases that are exacerbated by heat, perspiration, and bacterial colonization, especially in intertriginous regions.

BoNTA has been touted for a broad range of dermatologic, ophthalmologic, neurologic, urologic, gynecologic, and gastrointestinal applications because of its high efficacy and safety profile. BoNTA was approved by the US FDA for the treatment of strabismus and blepharospasm in 1989, for moderate to severe glabellar lines in 2002, for severe axillary hyperhidrosis in 2004, for migraines in 2010, for lateral canthi lines in 2013, and for forehead lines in 2017. Although numerous reports have demonstrated off-label clinical uses of BoNTA, no universally accepted treatment protocols exist. Standardization for dilution, dosing, timing, and injection techniques for off-label treatment of dermatologic conditions is needed. This article primarily investigates and analyzes the published literature on alternative therapeutic

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applications of BoNTA in dermatology (Table 1). MEDLINE was searched from January 2000 to December 2019 for articles published in English on the off-label uses of botulinum toxin in dermatology. All studies that met the criteria were included and summarized in this review using the 2011 Oxford Centre for Evidence-Based Medicine grading system [2]. Unless otherwise specified, BoNTA refers to onabotulinumtoxin A throughout this review.

2 Sweat Reduction

Botulinum toxin type A is indicated for the reduction of sweating. Table 2 lists the results of studies in this area.

2.1 Bromhidrosis and Malodor

Bromhidrosis and malodor are characterized by foul body odor stemming from bacterial colonization. In a randomized controlled trial (RCT) by Wu et al. [3], 19 patients with axillary bromhidrosis received intradermal injections of 200 IU abo-BoNTA to one axilla and normal saline to the other. At 3-month follow-up, a significant diminution of malodor and sweat secretion as well as atrophy and hypoplasia of apocrine glands was observed in the abo-BoNTA injection sites [3]. In an earlier RCT of 16 patients with axillary bromhidrosis treated with intracutaneous injections of 100 IU abo-BoNTA to one axilla and normal saline to the other, Heckmann et al. [4] observed significant diminution of odor intensity in the abo-BoNTA-treated axilla 1 week after treatment. Similar results were observed in several prospective studies of patients with primary, secondary, and adolescent axillary bromhidrosis as well as a case report of a patient with recalcitrant genital malodor [5–9].

2.2 Chromhidrosis

Chromhidrosis is characterized by pigmented yellow, green, blue, or black sweat, primarily involving the face and axillae. Case reports have demonstrated improvement of chromhidrosis following intradermal injections of BoNTA. Doses of 10–15 IU per cheek and 50 IU per axilla resulted in complete remission averaging 4–6 months [10–13].

2.3 Craniofacial Hyperhidrosis

In a prospective study, ten male patients with frontal hyperhidrosis received 86 IU BoNTA to the frontalis; all patients exhibited significant sweat reduction 4 weeks after treatment, and nine sustained improvement for 5 months [14]. Several case reports and case series in patients with varying craniofacial hyperhidrosis reported similar improvements sustained for 5–6 months after treatment [15–18].

2.4 Eccrine Nevus

Eccrine nevus is a rare skin hamartoma characterized by large areas of focalized hyperhidrosis. In a case study by Lera et al. [19], a patient with a congenital eccrine nevus on the forearm and severe hyperhidrosis received 100 IU BoNTA and exhibited reduced perspiration until retreatment 9 months later.

Eccrine angiomatous hamartoma is an extremely rare form of eccrine nevus with vascular proliferation. A 44-year-old man with an eccrine angiomatous hamartoma on the left upper back received 100 IU BoNTA and reported reduced localized perspiration and improved quality of life 1 year after treatment [20].

Table 1 Off-label dermatological uses for botulinum toxin type A

Dermatologic use	Dermatologic condition
Sweat reduction	Bromhidrosis, chromhidrosis, craniofacial hyperhidrosis, eccrine nevus, Frey's syndrome, focal anal hyperhidrosis, granulosis rubra nasi, HS, inverse psoriasis, palmoplantar hyperhidrosis, pompholyx
Pain/pruritus reduction	Anal fissure, brachioradial pruritus, bruxism, burn-induced pruritus, cutaneous leiomyomas, erosive lichen planus, Fox–Fordyce disease, frostbite neuralgia, granular parakeratosis, histamine-induced pruritus, lichen simplex chronicus, neuropathic scar pain, postherpetic neuralgia, RP, vulvodynia
Cosmetic enhancement	Décolleté wrinkles, facial asymmetry/synkinesis, facial flushing/erythema, gastrocnemius muscle hypertrophy, GS, leonine facies, masseter muscle hypertrophy, oily skin/enlarged pores, pectoral muscle contraction, salivary gland hypertrophy, scar prevention, scar treatment, temporalis muscle hypertrophy, trapezius muscle hypertrophy
Hair growth	Androgenetic alopecia, cephalalgic alopecia, folliculitis decalvans, radiation-induced alopecia
Miscellaneous	Apocrine hidrocystomas, aquagenic keratoderma, Darier's disease, eccrine hidrocystomas, epidermolysis bullosa simplex, Hailey–Hailey disease, linear IgA, PC, plaque psoriasis

GS gummy smile, *HS* hidradenitis suppurativa, *IgA* immunoglobulin A, *PC* pachyonychia congenita, *RP* Raynaud's phenomenon

Table 2 Sweat reduction with botulinum toxin type A

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration[a]	Results
Bromhidrosis/malodor	RCT (II) [3]	200 IU abo-BoNTA/axilla vs. normal saline	3	SI
	RCT (II) [4]	100 IU abo-BoNTA/axilla vs. normal saline	1 wk	CR
	PS (IV) [5–8]	50–100 IU/axilla	1–12	SI
	CRep (IV) [9]	100 IU (perineum)	9	SI
Chromhidrosis	CRep (IV) [10–12]	10–15 IU/cheek	4–5	Improvement/CR
	CRep (IV) [13]	50 IU/axilla	6	CR
Craniofacial hyperhidrosis	PS (IV) [14], CRep (IV) [15]	33–86 IU (brow)	5	CR
	CRep (IV) [16]	60 IU (frontal scalp)	6	CR
		12 IU (upper lip/chin)	6	CR
	CRep (IV) [16, 17]	20–100 IU (central face)	6	CR
	CS (IV) [18]	20 IU (nose)	6	CR
Eccrine nevus	CRep (IV) [19]	100 IU (forearm)	9	CR
	CRep (IV) [20]	100 IU (back)	12	CR
Frey's syndrome	RS (III) [21]	30 IU BoNTA (parotid gland)	12	CR
		35 IU inco-BoNTA (parotid gland)	12	CR
		200 IU abo-BoNTA (parotid gland)	12	CR
	CRep (IV) [22, 23]	18–50 IU (parotid gland/cheeks)	12–25	CR
	CRep (IV) [24]	100 IU (right temple region)	≥3	CR
	CRep (IV) [16]	80 IU (parotid gland/cheeks)	6–8	CR
Focal anal hyperhidrosis	PS [25]	30–54 IU (anal fold)	1	SI
Granulosis rubra nasi	CRep (IV) [26]	20 IU (nose)	6–12	SI
Hidradenitis suppurativa	CRep (IV) [27, 28]	50–100 IU/axilla	3–10	CR
	CRep (IV) [27]	100 IU (groin/inner thighs)	6	CR
	CRep (IV) [29]	100 IU/axilla	3	SI
		100 IU/submammary area	3	SI
		100 IU/inguinal fold	3	SI
	CRep (IV) [30]	125 IU abo-BoNTA/axilla	10	Improvement
	CRep (IV) [31]	40 IU (prepubertal inguinal folds)	6	CR
Inverse psoriasis	PS (IV) [32]	50–100 IU (axilla/submammary sulcus/umbilicus/intergluteal folds/ inguinal folds)	3–4	CR
	CRep (IV) [33]	75 IU/axilla	2	CR
Palmoplantar hyperhidrosis	RCT (II) [34]	50 IU BoNTA/palm vs. 100 IU BoNTA/palm	2–6	SI in both groups
	RCT (II) [35]	100 IU/palm vs. normal saline	1	CR in BoNTA group
	RCT (II) [36]	66–72 IU BoNTA/palm vs. 272–295 IU abo-BoNTA/palm	1–3	Improvement in both groups
	RCT (II) [37]	100–150 IU BoNTA/palm vs. 100–150 IU inco-BoNTA/palm	3–6	Similar efficacy and duration for both groups
	PS (IV) [38–42]	50–200 IU/palm	6–22	SI
	RS (III) [43]	250 IU abo-BoNTA/palm	7–9.5	SI
	PS (IV) [40, 44–46]	50–250 IU BoNTA/sole (adult)	3–6	SI
	PS (IV) [47]	75–100 IU BoNTA/sole (juvenile)	6	SI
Pompholyx	Prospective controlled studies (III) [48, 49], case study (IV) [50]	100–162 IU/palm	≥2	SI

abo-BoNTA abobotulinumtoxin A, *BoNTA* botulinum toxin type A, *CR* complete response, *CRep* case report, *CS* case series, *PS* prospective study, *RCT* randomized controlled trial, *RS* retrospective study, *SI* sustained improvement, *wk* week(s)

[a]Duration is presented in months unless otherwise indicated

2.5 Frey's Syndrome

Frey's syndrome is a neurological disorder that occurs after trauma to the parotid gland and results in sweating, erythema, and warmth upon gustatory stimuli. BoNTA injections represent a first-line treatment for Frey's syndrome. A retrospective study by Jansen et al. [21] evaluated 100 patients with Frey's syndrome who received 440 intracutaneous injections of BoNTA, inco-BoNTA, or abo-BoNTA. Patients received a median of 30 IU BoNTA (range 18.6–46), 35 IU inco-BoNTA (range 22.6–46.8), or 200 IU abo-BoNTA (range 88.8–318.6) over the course of a median of four treatments at a median of 12-month intervals. Injection doses did not significantly alter among treatments, and repeated treatments did not correlate with increased duration of efficacy. The authors concluded that BoNTA was a consistent and effective treatment for Frey's syndrome [21]. Several case reports described the efficacy of 18–80 IU BoNTA for the reduction of gustatory sweating and erythema sustained for 6–25 months after treatment [16, 22–24].

2.6 Focal Anal Hyperhidrosis

In a prospective study, 11 male patients with focal hyperhidrosis of the anal fold received 30–54 IU BoNTA placed in aliquots of 1 IU/cm^2. After 4 weeks, a significant 78.5% reduction in hyperhidrotic area as well as high patient satisfaction was observed [25].

2.7 Granulosis Rubra Nasi

Granulosis rubra nasi is a genetic disorder of the eccrine glands defined by focal hyperhidrosis of the central face and diffuse facial erythema. A 16-year-old male with granulosis rubra nasi received intradermal injections of 20 IU BoNTA placed at the nose. Diminished nasal perspiration and erythema were maintained for 6 months after treatment. Reoccurrence was observed 12 months after initial treatment [26].

2.8 Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is an inflammatory condition affecting the follicular epithelium and apocrine glands of the axillae and groin. Several reports have described sustained improvement of HS symptoms for 3–10 months following application of 50–100 IU BoNTA to each axilla, 125 IU abo-BoNTA to each axilla, 100 IU BoNTA to each submammary area, and 100 IU BoNTA to the groin [27–30]. A case report described a 7-year-old girl with prepubertal HS who received 40 IU BoNTA injected intradermally at the inguinal folds and exhibited complete remission for 6 months [31].

2.9 Inverse Psoriasis

The use of BoNTA to diminish local sweat production and thereby skin maceration, inflammation, pain, and hyperkeratosis in the treatment of inverse psoriasis has been efficacious. In a prospective study, 15 patients with inverse psoriasis at the axillae, submammary sulcus, intergluteal folds, inguinal folds, and umbilicus received 2.4 IU aliquots of a total 50–100 IU BoNTA. After 3 months, all patients reported diminished pain and pruritus, and 13 patients displayed decreased maceration and erythema [32]. A male patient with concomitant axillary hyperhidrosis and inverse psoriasis demonstrated improvement following treatment with 75 IU BoNTA per axilla [33].

2.10 Palmoplantar Hyperhidrosis

2.10.1 Palmar Hyperhidrosis

Several reports described successful treatment of palmar hyperhidrosis following intradermal injections of 2–5 IU aliquots of 50–200 IU BoNTA placed in a 1 cm interval grid pattern on the palmar surface of each hand [34–42]. Saadia et al. [34] performed an RCT in 24 patients with palmar hyperhidrosis who received 50 or 100 IU BoNTA per palm. All patients exhibited a significant decrease in sweating 2 months after treatment, and the majority of patients in both groups sustained the anhidrotic effect for 6 months after treatment [34]. In an RCT by Lowe et al. [35], 19 patients received intradermal injections of 100 IU BoNTA to one hand and saline to the other. Significant improvement in the BoNTA-treated hand was observed 28 days after treatment [35]. Simonetta Moreau et al. [36] observed similar efficacy with BoNTA and abo-BoNTA using a dosage conversion of 1:4 in a double-blind RCT of eight patients with primary palmar hyperhidrosis [36]. In a double-blind RCT, 25 patients with palmar hyperhidrosis received intradermal injections of 100–150 IU BoNTA and 100–150 IU inco-BoNTA to contralateral hands. No significant difference in anhidrotic efficacy or duration was observed between the BoNTA- or inco-BoNTA-treated hands 3–6 months after treatment [37]. In an 11-year retrospective study of 28 patients with palmar hyperhidrosis [43], repeated intradermal injections of 250 IU abo-BoNTA per palm significantly extended the median treatment efficacy from 7 to 9.5 months.

2.10.2 Plantar Hyperhidrosis

For the treatment of plantar hyperhidrosis, 50–250 IU BoNTA per sole demonstrated anhidrotic efficacy for an average of 6 months after treatment [40, 44–47]. Bernhard et al. [47] investigated the efficacy of BoNTA for the treatment of 15 adolescents with plantar hyperhidrosis; 11

patients experienced improvement after receiving 2.5 IU aliquots of 75–100 IU BoNTA placed in 20–40 injection sites per sole for 6 months after treatment.

2.11 Pompholyx

Pompholyx (dyshidrotic eczema) is a relapsing vesicular-bullous condition affecting the palms or soles. Treatment with 100–162 IU BoNTA per palm has been associated with significant reduction in perspiration, pruritus, and vesiculation 2 months after treatment [48–50]. The literature search found no studies that investigated the use of BoNTA for plantar holyx.

3 Pain/Pruritus Reduction

Botulinum toxin type A is indicated for the reduction of pain and pruritus (see Table 3).

3.1 Anal Fissure

Efficacy rates of up to 96% have been reported with the use of BoNTA in the treatment of anal fissure [105]. Treatment with 20–100 IU BoNTA placed in unilateral, bilateral, and circumferential injections around the anal fissure has been reported [51–54]. In an RCT, 100 patients with chronic anal fissure received bilateral injections of 50 IU abo-BoNTA per side or unilateral injections of 100 IU abo-BoNTA to the internal anal sphincter. Abo-BoNTA injections were equally effective in inducing healing of anal fissures in both groups; however, patients in the unilateral group demonstrated greater improvement in fissure pain 12 months after treatment [51]. Berkel et al. [52] observed significant improvement of chronic anal fissures following treatment with abo-BoNTA compared with isosorbide dinitrate ointment (ISDN). Abo-BoNTA-treated patients received a single treatment with 60 IU abo-BoNTA injected at the internal anal sphincter. At 2 months after treatment, 18 of 27 patients in the abo-BoNTA group exhibited complete resolution of anal fissures. However, 27% of abo-BoNTA-treated patients and 50% of ISDN-treated patients demonstrated reoccurrence 1 year after treatment [52]. In a retrospective study, patients received 25 IU BoNTA injected in 12.5 IU aliquots on both sides of fissures at the intersphincteric groove or the internal anal sphincter. At 3 months after treatment, 76.1% exhibited a satisfactory response; 5 years after treatment, 64.8% of patients remained in complete remission [53]. In another retrospective study [54], 158 patients with chronic anal fissure received a low-dose treatment of 20–40 IU BoNTA or a high-dose treatment of 80–100 IU BoNTA. Treatment was administered in aliquots of 20 IU BoNTA placed unilaterally, bilaterally, or circumferentially around the fissure. Patients in both groups exhibited improvement 2 months after treatment. Patients in the high-dose group exhibited greater patient satisfaction and lower reoccurrence rates 6–24 months after treatment [54]. This observed dose-dependent efficacy of BoNTA [54] is incongruent with the results of a meta-analysis by Bobkiewicz et al. [105], which determined dose-independent efficacy of BoNTA for the treatment of anal fissure.

3.2 Brachioradial Pruritus

A woman with recalcitrant brachioradial pruritus received 100 IU BoNTA intradermally injected into the neck, scapular regions, and upper posterior arms. The patient received four total treatments and sustained improvement for 6 months after the final treatment [55].

3.3 Bruxism

Bruxism is characterized by teeth grinding and masseteric clenching. Treatment with BoNTA to the masseter and/or temporalis muscles reduces the frequency of bruxism episodes, pain, and occlusal force. Jadhao et al. [56] performed an RCT in 24 patients with bruxism. Patients who received 30 IU BoNTA per masseter and 20 IU per temporalis exhibited a significant decrease in maximum occlusal force compared with those receiving saline placebo and control groups [56]. In an RCT, 20 patients with bruxism and myofascial pain received either 30 IU BoNTA per masseter and 20 IU BoNTA per temporalis or equivalent saline. BoNTA-treated patients demonstrated a significant decrease in masticatory pain and improvement in subjective efficacy 6 months after treatment [57]. In a study by Zhang et al. [58], 30 patients with temporomandibular disorder and associated bruxism received either 25 IU BoNTA per masseter, saline placebo, or no treatment. BoNTA-treated patients exhibited a significant decrease in occlusal force and increase in biting time compared with the other groups 3 months after treatment [58]. In an RCT by Al-Wayli [59], 50 patients with nocturnal bruxism received 20 IU BoNTA per masseter or traditional treatment (behavioral therapy, occlusal splints, or drugs). The BoNTA group exhibited a significant decrease in masseter pain and number of bruxism events compared with the control group [59]. Ondo et al. [60] performed an RCT in 31 patients with sleep bruxism and observed significant improvement in the BoNTA groups measured using Clinical Global Impression and visual analog scale scores. The number of bruxism episodes decreased in the BoNTA group and increased in the placebo group, but no significant difference was found between the two groups [60]. In an RCT by Lee et al. [61], 12 patients with nocturnal bruxism received 40 IU abo-BoNTA per masseter or equivalent saline. Abo-BoNTA-treated patients exhibited a significant decrease in

Table 3 Pain/pruritus reduction with botulinum toxin A

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration[a]	Results
Anal fissure	RCT (II) [51]	100 IU abo-BoNTA (internal anal sphincter) unilateral injections vs. bilateral injections	12	SI
	RCT (II) [52]	60 IU abo-BoNTA (internal anal sphincter) vs. isosorbide dinitrate ointment	2–12	SI
	RS (IV) [53]	25 IU (internal anal sphincter/intersphincteric groove)	6–60	SI
	RS (IV) [54]	20–40 vs. 80–100 IU (internal anal sphincter)	6–24	SI
Brachioradial pruritus	CRep (IV) [55]	100 IU (neck/upper posterior arms/scapular regions)	6	SI
Bruxism	RCT (II) [56]	30 IU/masseter, 20 IU/temporalis vs. normal saline vs. no treatment	3–6	SI
	RCT (II) [57]	30 IU/masseter, 20 IU/temporalis vs. normal saline	6	SI
	RCT (II) [58]	25 IU/masseter vs. normal saline vs. no treatment	6	Significant improvement in occlusal force/bite time
	RCT (II) [59]	20 IU/masseter vs. traditional therapy	1–12	Reduced pain and bruxism episodes in BoNTA group
	RCT (II) [60]	60 IU/masseter, 40 IU/temporalis vs. normal saline	1–2	Improvement in BoNTA group. No significant difference in number of bruxism episodes
	RCT (II) [61]	40 IU abo-BoNTA/masseter vs. normal saline	3–12	Decreased bruxism episodes in masseter muscle
Burn-induced pruritus	PS (IV) [62]	10–25 IU (burn lesions)	9	CR
Cutaneous leiomyomas	RCT (II) [63]	< 300 IU total, 5 IU per 1 cm^2 leiomyoma (neck/torso/extremities) vs. normal saline	1–3	Improvement in both groups
	CRep (IV) [64, 65]	200 IU (leiomyomas)	3	SI
Erosive lichen planus	CRep (IV) [66]	40–60 IU (vulvar vestibule)	2–3	SI
Fox–Fordyce disease	CRep (IV) [67]	50 IU/axilla	8	SI
Frostbite neuralgia	CRep (IV) [68]	60 IU/palm	1–2	SI
Granular parakeratosis	CRep (IV) [69]	50 IU/axilla	6	CR
Histamine-induced pruritus	RCT (II) [70]	5 IU (forearm) vs. normal saline	7 days	CR
Lichen simplex chronicus	CS (IV) [71]	20–80 IU abo-BoNTA (lichenoid lesions)	4	CR
Neuropathic scar pain	CRep (IV) [72]	50 IU (left upper arm scar)	5	SI
	CRep (IV) [73]	30 IU (glabella scar)	24	SI
Postherpetic neuralgia	RCT (II) [74]	100 IU (affected areas), 5 IU/point vs. normal saline	4	SI
	RCT (II) [75]	< 200 IU (affected areas), 5 IU/point vs. lidocaine vs. normal saline	3	SI
	RCT (II) [76]	20–190 IU (affected areas) vs. normal saline	3–4	SI
	PS (IV) [77], CS [78], CRep (IV) [79–81]	50–200 IU (affected areas)	2–6	SI
	CRep (IV) [82]	100 IU (left orbital region)	6	SI

Table 3 (continued)

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration[a]	Results
Raynaud's phenomenon	RCT (II) [83]	40 IU/palm vs. normal saline	6 wk	Increased digital pulp temperature in BoNTA-treated hands
	PS (IV) [84, 85], RS (IV) [86–90], CRep (IV) [91, 92]	36–100 IU/palm	4–60	SI
	CRep (IV) [93]	300 IU abo-BoNTA/palm	2	SI
	RCT (II) [94]	50 IU/dorsal hand vs. normal saline	1, 4	Reduced blood flow in BoNTA-treated hands
	PS (IV) [95]	50 IU/dorsal hand	1–3	SI
	CS (IV) [96]	10 IU/sole	5	SI
	CS (IV) [97]	80–100 IU/sole	6	SI
Vulvodynia	RCT (II) [98]	20 IU (bulbospongiosus muscle) vs. normal saline	3–6	No improvement over placebo
	RCT (II) [99]	50 IU (dorsal vulvar vestibulum) vs. 100 IU vs. normal saline	6	Significant improvement following repeat treatments of 100 IU
	RS (III) [100]	100 IU (levator ani muscle)	6	SI
	RS (IV) [101]	40–100 IU (introitus) vs. gabapentin	6–24	SI in both groups
	PS (IV) [102]	20–40 IU (vestibule/levator ani muscle/perineal body)	4–24	SI
	PS (IV) [103]	100 IU (bulbospongiosus muscle)	3–6	SI
	CRep (IV) [104]	24 IU (introitus)	12	CR

abo-BoNTA abobotulinumtoxin A, *BoNTA* botulinum toxin type A, *CR* complete response, *CRep* case report, *CS* case series, *PS* prospective study, *RCT* randomized controlled trial, *RS* retrospective study, *SI* sustained improvement, *wk* weeks

[a]Duration is months unless otherwise noted

bruxism frequency in the masseter muscle 1–3 months after treatment [61].

3.4 Burn-Induced Pruritus

In a prospective study, nine patients with severe pruritus secondary to burns received 10–25 IU BoNTA. Within 1 month of treatment, patients reported a decrease in severity of pruritus from > 7 to 0 on a 10-point scale. Complete remission was sustained an average of 9 months after treatment [62].

3.5 Cutaneous Leiomyomas

Cutaneous leiomyomas are benign but often very painful smooth muscle neoplasms. In an RCT, patients received injections of 5 IU BoNTA or saline per 1 cm^2 of lesion. Although a significant difference in average lesional pain was not observed between BoNTA and placebo groups, a significant improvement in subjective dermatologic pain and quality of life was observed in the BoNTA group 1 month after treatment [63]. Two earlier case reports of patients with cutaneous leiomyomas described sustained improvement following treatment with BoNTA [64, 65].

3.6 Erosive Lichen Planus

Erosive lichen planus is a rare inflammatory condition characterized by chronic painful, raw lesions in the vulvovaginal area. A woman with erosive lichen planus received 40 IU BoNTA injected in 20 IU aliquots at each side of the vulvar vestibule. She experienced diminished pain and burning sensations for 2 months. She was re-treated with 60 IU BoNTA injected in 30 IU aliquots at each side of the vulvar vestibule and sustained improvement for 3 months [66].

3.7 Fox–Fordyce Disease

Fox–Fordyce disease is a rare inflammatory condition of the apocrine glands exasperated by sweating. A patient with refractory Fox–Fordyce disease received intradermal injections of 50 IU BoNTA per axilla. The patient exhibited a complete resolution of pruritic symptoms and decreased

number of follicular papules sustained for 8 months after treatment [67].

3.8 Frostbite Neuralgia

A case report described a Caucasian soldier with 2-year frostbite sequelae on his hands who received 12 IU aliquots for a total dose of 60 IU BoNTA per hand. Reduced pain as well as increased hand temperature, sensory function, and cold tolerance was observed 3 weeks after treatment. Angiography confirmed post-treatment dilation of digital arteries. The patient received a second treatment of 60 IU BoNTA and sustained further improvement 6 weeks after treatment [68].

3.9 Granular Parakeratosis

Granular parakeratosis is a rare condition characterized by pruritic erythematous, hyperpigmented plaques at the intertriginous regions. A 44-year-old woman with axillary granular parakeratosis treated with 50 IU BoNTA per axilla exhibited complete resolution of plaques and sustained improvement for 6 months after treatment [69].

3.10 Histamine-Induced Pruritus

In a double-blind controlled trial, 14 male patients with histamine-induced itch on the forearms were treated with subcutaneous injections of 5 IU BoNTA on the volar surface of one forearm and saline on the other. Assessments were performed 1, 3, and 7 days after treatment. At all assessment intervals, the BoNTA-treated forearm exhibited significantly reduced itch intensity compared with control. At day 7, the BoNTA-treated forearm exhibited significantly reduced duration of itch compared with control and pretreatment levels as well as significantly reduced histamine-induced flare areas compared with control. Additionally, at days 3 and 7, the BoNTA-treated arm displayed significantly reduced vasomotor reaction and neurogenic inflammation compared with day 1 and the control [70].

3.11 Lichen Simplex Chronicus

Lichen simplex chronicus is an atopic dermatitis associated with recalcitrant pruritus. In a case series, four patients with lichenoid patches on the lower legs were treated with intradermal injections of 20 IU abo-BoNTA per 2 cm^2 lesion (20–80 IU abo-BoNTA total). Patients experienced complete resolution of pruritus and lichenoid lesions for 4 months after treatment [71].

3.12 Neuropathic Scar Pain

Two case reports described the efficacy of BoNTA for treating neuropathic scar pain. A woman with a neuropathic pain in a normotrophic scar from a melanoma excision at the left upper arm 5 years prior received treatment with a total dose of 50 IU BoNTA injected intradermally within and along the periphery of the scar. She exhibited 50% pain reduction within 1 month of treatment and sustained improvement for 5 months [72]. Another patient experienced refractory neuropathic scar pain following Mohs surgery of a squamous cell carcinoma. She received 30 IU BoNTA to the scar and exhibited diminished pain sustained for 2 years after treatment [73].

3.13 Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a complication of herpes zoster that can result in chronic, debilitating pain. Treatment with 50–200 IU BoNTA injected subcutaneously or intradermally in a chessboard or fanning pattern has been effective for reducing PHN pain and pruritus for 2–9 months after treatment [74–82]. In an RCT by Xiao et al. [75], 60 patients with PHN received subcutaneous injections of either BoNTA, lidocaine, or placebo. The BoNTA group exhibited significantly reduced pain, improved sleep, and reduced opioid use compared with the lidocaine and saline placebo groups. Improvement was sustained for 3 months [75]. In another RCT in which 30 patients received either BoNTA or saline, the BoNTA group exhibited significant improvement in pain and sleep scores that was sustained for 16 weeks [74]. Ranoux et al. [76] observed similar results in an earlier RCT.

3.14 Raynaud's Phenomenon

Raynaud's phenomenon (RP) is an exaggerated vasospastic disorder affecting the extremities that is triggered by cold temperatures and stress. BoNTA has been touted as an effective therapeutic tool for the treatment of primary and secondary RP.

Several studies have investigated the palmar injection site approach through digital injections targeting the neurovascular bundle, palmar injections targeting the palmar arch and web space, or distal volar wrist injections of the proximal hand. A retrospective case series of 26 patients with either primary or secondary RP found no significant difference in efficacy among these three palmar injection techniques [86]. In an RCT, eight patients received 40 IU BoNTA or saline placebo to contralateral hands placed in four injection points targeting the superficial palmar arch. The BoNTA group displayed a significant increase in digital pulp temperature compared with placebo [83]. Several

prospective and retrospective studies described the efficacy of 40–100 IU BoNTA or 300 IU abo-BoNTA injected using the palmar approach for the treatment of RP, including a case report of a woman with RP, rheumatoid arthritis, and systemic lupus erythematosus [84–93]. However, hand muscle weakness from lumbricals malfunction and dysesthesia has been reported following palmar injections [85–88].

To avoid reported hand muscle weakness and pain following proximal and distal palmar injections, Quintana-Castanedo et al. [106] recommended interdigital injections of 4–8 IU aliquots of 32 IU BoNTA per hand, avoiding the thumb web space, for improvement of RP sustained 10–12 months after treatment. Medina et al. [90] performed a 3-year retrospective study of 15 patients with primary RP or RP secondary to limited systemic scleroderma, diffuse systemic scleroderma, or mixed connective tissue disease. Patients received 32–64 IU per hand infiltrated at the lateral aspects of each digit except the first. A significant reduction in pain and weekly RP episodes was observed within 1 month of treatment [90].

Two studies have investigated the efficacy of dorsal BoNTA injections. An RCT assessed the therapeutic effect of dorsal BoNTA injections on blood flow in 20 patients with RP secondary to scleroderma. Patients received 50 IU BoNTA per hand injected dorsally around the digital neurovascular bundles. BoNTA-treated patients exhibited significantly decreased blood flow 1 month after treatment, but no significant change in blood flow between groups was observed 4 months after treatment. The authors noted that patients with longstanding RP and diffuse scleroderma primarily influenced this difference. However, patients reported a significant reduction in RP symptom severity for BoNTA-treated hands compared with placebo at 1 and 4 months after treatment [94]. In a prospective case series, 40 patients with RP secondary to systemic sclerosis received 50 IU BoNTA per hand injected dorsally around the digital neurovascular bundles in two injections per web space. Patients demonstrated a significant reduction in pain, swelling, cold intolerance, color change, and RP attacks as well as increased hand strength for 1–3 months after treatment [95]. The mixed results for the efficacy of the dorsal approach could be attributed to the heterogeneity in injection technique, follow-up intervals, and outcome measures [94, 95].

Two reports described the efficacy of BoNTA for the treatment of patients with RP secondary to scleroderma in the toes. Three patients with RP secondary to scleroderma in the toes received 10 IU BoNTA per foot injected in aliquots of 2 IU at the base of each digit. Patients reported improved cold intolerance and color change as well as reduced frequency and severity of RP attacks lasting 5 months after treatment [96]. A woman with ischemic and necrotic ulcers on the toes received 8–10 IU aliquots of 80–100 IU BoNTA injected into the base sides of each digit. Immediate improvement of pain, temperature, and color was sustained for 6 months after treatment [97].

3.15 Vulvodynia

Vulvodynia is an idiopathic chronic pain syndrome characterized by pruritus, stinging, and burning sensations as well as dyspareunia. Several studies described the antinociceptive effects of BoNTA injections for treatment of vulvodynia [98–104]. In an RCT, 64 women with vulvodynia received either 20 IU BoNTA or saline injected into the bulbospongiosus muscle. The BoNTA group did not show significant reduction in pain or improved sexual functioning or quality of life compared with placebo 3 and 6 months after treatment [98]. Despite this report, several later cases demonstrated the efficacy of BoNTA as a therapeutic tool for the treatment of vulvodynia. In an RCT by Diomande et al. [99], 33 patients with provoked vulvodynia received 50 or 100 IU BoNTA or saline injected subcutaneously into the dorsal vulvar vestibulum. Symptomatic patients received subsequent treatment with 100 IU BoNTA over a 6-month period. No significant difference was observed between BoNTA and placebo groups 3 months after the initial treatment, but repeat high doses of 100 IU BoNTA significantly reduced pain over a 6-month period [99]. In a retrospective study of 79 patients with refractory vulvodynia, Hedebo Hansen et al. [100] observed sustained improvement for 6 months following treatment with 100 IU BoNTA [100]. In a retrospective study by Jeon et al. [101], the efficacy of BoNTA injections was compared with that of gabapentin: 11 patients with vulvodynia received 20 IU aliquots of 40–100 IU BoNTA injected into the submucosal layer of the introitus. After 1 month, a second round of injections was administered to five remaining symptomatic patients. It is important to note that the two patients who received initial treatment with 100 IU BoNTA did not need retreatment after 4 weeks. Patients in both groups experienced significant pain reduction for a mean of 12 months after treatment [101]. Pelletier et al. [103] described 20 patients with provoked vulvodynia who received 100 IU BoNTA injected into the bulbospongiosus muscle. Pain diminished in 80% of patients, and this was sustained for 6 months after treatment [103].

4 Cosmetic Enhancement

Table 4 details conditions in which botulinum toxin type A has been used for cosmetic enhancement.

Table 4 Cosmetic enhancement with botulinum toxin type A

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration[a]	Results
Décolleté wrinkles	CS (IV) [107]	75–120 IU abo-BoNTA (lower platysma)	2 wk	SI
Facial asymmetry/synkinesis	RCT (II) [108]	Abo-BoNTA vs. ona-BoNTA vs. inco-BoNTA (synkinetic areas) 3:1:1 dosage ratio	1, 2, 4 wk	SI
	Prospective cohort study (III) [109]	12.5–35 IU (face/neck)	3	SI
Facial flushing/erythema	RCT (II) [110]	15 IU pra-BoNTA/cheek vs. normal saline	2	SI
	RCT (II) [111]	10 IU inco-BoNTA/cheek vs. normal saline	4	SI
	RCT (II) [112]	500 IU abo-BoNTA (face/neck/chest/scalp) vs. normal saline	2–6	SI
	PS (IV) [113, 114]	10–15 IU/cheek	2	SI
	PS (IV) [115]	100 IU (neck/chest wall)	1	SI
	PS (IV) [116]	15–45 IU abo-BoNTA (brow/nose/cheeks/chin)	3	SI
Gastrocnemius muscle hypertrophy	Prospective randomized comparative study (III) [117]	80 vs. 100 IU pra-BoNTA/calf	6	Improvement in all groups
	Prospective double-blind comparative study (III) [118]	100 IU BoNTA/calf vs. 100 IU pra-BoNTA/calf	6	Improvement in both groups
	PS (III–IV) [119–121]	32–100 IU/calf	6	SI
	CS (IV) [122]	300–360 IU abo-BoNTA/calf	6	SI
	CRep (IV) [123]	200 IU pra-BoNTA/calf	3	SI
GS: anterior	PS (IV) [124]	2.5–5 IU abo-BoNTA (nasolabial fold)	3–5	SI
GS: posterior	PS (IV) [124]	2.5 IU abo-BoNTA (2 points in malar region)	3–5	SI
GS: mixed	PS (IV) [124]	2.5 IU abo-BoNTA (3 points in malar/nasal ala regions)	3–5	SI
	CRep (IV) [125]	2 IU (2 points in levator labii superioris), 5 IU/minor zygomaticus	5	SI
GS: asymmetric	PS (IV) [124]	2.5 IU abo-BoNTA (2 points in malar region on hyperkinetic side)	3–5	SI
Leonine facies	CS (IV) [126]	70–80 IU (procerus/corrugators/brow)	2–6	SI
Masseter muscle hypertrophy	RCT (II) [127], follow-up study (III) [128], case-controlled study (IV) [129], PS (IV) [130–132]	20–40 IU/masseter	3–9	SI
	Randomized double-blind split-face controlled trial (II) [133]	25 IU BoNTA/masseter vs. 25 IU inco-BoNTA/masseter	4	Improvement in both groups
	Prospective randomized comparative study (IV) [134]	25 IU BoNTA/masseter vs. 25 IU pra-BoNTA/masseter	6	Improvement in both groups
	Prospective blinded randomized study (IV) [135]	40 IU inco-BoNTA/masseter	5	SI
	Retrospective/follow-up studies (III) [136, 137], PS (IV) [138]	100–150 IU abo-BoNTA/masseter	3–25	SI

Table 4 (continued)

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration[a]	Results
Oily skin/enlarged pores	Prospective split-face controlled study (III) [139]	15 IU BoNTA/cheek vs. normal saline	4	SI
	Prospective randomized double-blind study (III) [140]	10 vs. 20 IU (frontalis)	4	SI
	PS (IV) [141]	30–45 IU abo-BoNTA (frontalis)	3	SI
Pectoral muscle contraction	CRep (IV) [142]	75 IU/pectoralis	1	CR
	CRep (IV) [143]	100 IU/pectoralis	3–6	CR
Salivary gland hypertrophy	CS (IV) [144]	30–38 IU/parotid gland, 20 IU/submandibular gland	4–6	SI
	CS (IV) [145]	20–100 IU/parotid gland, 30–100 IU/masseter	5–6	SI
Scar prevention: facial wounds	RCT (II) [146]	15–80 IU (facial surgical incision) 10 IU/cm scar vs. normal saline	6	Decreased scar height and width
	RCT (II) [147]	17–50 IU pra-BoNTA (forehead laceration) vs. no treatment	6	Improved cosmesis
	RCT (II) [148]	15–40 IU (facial wound) vs. no treatment	12	Improved cosmesis
	RCT (II) [149]	30 IU (2–4 cm forehead wound) vs. normal saline	6	Improved cosmesis
Scar prevention: post-epicanthoplasty	RCT (II) [150]	5 IU (medial canthi) vs. normal saline	3–6	Improved cosmesis
Scar prevention: post-cheiloplasty	RCT (II) [151]	1 IU/kg (infant cheiloplasty scar) vs. normal saline	6	Improved cosmesis
	RCT (II) [152]	8 IU (infant cheiloplasty scar) 2 IU/kg maximum vs. normal saline	6	Improved cosmesis
	RCT (II) [153]	15 IU (adult cleft lip scar revision) vs. normal saline	6	Improved cosmesis
Scar prevention: post-thyroidectomy	RCT (II) [154]	20–65 IU (half thyroidectomy scar) vs. normal saline	6	Improved cosmesis
	RCT (II) [155]	60 IU pra-BoNTA (half thyroidectomy scar) operation day vs. 2-week postoperative	6	Improved cosmesis in operation-day injection side
	RCT (II) [156]	15 IU (half thyroidectomy scar) vs. normal saline	6–12	No improvement/SI in subgroup analysis
Scar prevention: post-sternotomy	RCT (II) [157]	50–70 IU (half sternotomy scar) vs. normal saline	6	Improved cosmesis/scar width in BoNTA halves
Scar treatment: keloids	RCT (II) [158]	5 IU BoNTA/cm^3 keloid vs. intralesional corticosteroid	7	Improved cosmesis
	RCT (II) [159]	1.5 IU/cm of keloid (total 12–24 IU) vs. intralesional corticosteroid	1, 3, 6	Significantly greater improvement in steroid group
	PS, single arm (IV) [160]	70–140 IU/keloid	3	SI
	PS, single arm (IV) [161]	70–140 abo-BoNTA IU/keloid	3	No significant improvement
	CS (IV) [162]	20–100 IU/keloid (cheek, neck, chest, or thigh)	2–43	Improved cosmesis
	CRep (IV) [163]	100 IU/keloid (anterior chest wall)	5 wk	Improved cosmesis
Scar treatment: hypertrophic scars	PS (IV) [164, 165]	2.5 IU/cm^3 hypertrophic scar, maximum 100 IU BoNTA	6	Improved cosmesis

Table 4 (continued)

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration[a]	Results
Temporal muscle hypertrophy	PS (IV) [166]	25 IU/temporal muscle	5–6	Improved cosmesis
	CRep (IV) [138]	100 abo-BoNTA/temporal muscle	15	Improved cosmesis
Trapezius muscle hypertrophy	PS (IV) [167]	50 IU/trapezius muscle	6–10	Improved cosmesis
	CS (IV) [168]	50 IU pra-BoNTA/trapezius muscle	4–5	Improved cosmesis

abo-BoNTA abobotulinumtoxin A, *BoNTA* botulinum toxin type A, *CR* complete response, *CRep* case report, *CS* case series, *GS* gummy smile, *inco-BoNTA* incobotulinumtoxin A, *ona-BoNTA* onabotulinumtoxin A, *pra-BoNTA* prabotulinumtoxin A, *PS* prospective study, *RCT* randomized controlled trial, *SI* sustained improvement, *wk* weeks

[a]Duration indicated in months unless otherwise indicated

4.1 Décolleté Wrinkles

Becker-Wegerich et al. [107] reported the efficacy of abo-BoNTA injection for the treatment of décolleté wrinkles. The author proposed targeting the muscle fibers of the lower platysma, which exert traction forces on the overlying dermis, resulting in horizontal and vertical décolleté wrinkles. In a case series, five patients received 15 IU aliquots of a total 90–120 IU abo-BoNTA placed at 2 cm intervals to the lower platysma; all exhibited diminished lines and wrinkles [107].

4.2 Facial Asymmetry/Synkinesis

BoNTA has been effective in the treatment of facial asymmetry and synkinesis due to Bell's palsy and vestibular schwannoma. A single-blind RCT compared the efficacy of abo-BoNTA, ona-BoNTA, and inco-BoNTA for the treatment of facial synkinesis. All three neuromodulators exhibited similar efficacy up to 4 weeks after treatment. However, the effect of inco-BoNTA was significantly lower than that of ona-BoNTA after 4 weeks [108]. Shinn et al. [109] observed the efficacy of BoNTA for the treatment of 99 patients with facial synkinesis. Patients were treated with 12.5–32.5 IU BoNTA to the corrugator, orbicularis oculi superioris, orbicularis oculi inferioris, mentalis, risorius, and platysma. Each facial muscle and the platysma was treated with 2–3 and 9–10 IU BoNTA, respectively. Patients received a median of three treatments of increasing doses at 3-month intervals [109].

4.3 Facial Flushing and Erythema

The efficacy of intradermal injection of BoNTA for the treatment of facial flushing and erythema primary or secondary to rosacea or menopausal hot flushes has been observed in several RCTs and prospective studies. In a double-blind split-face RCT, 24 patients with rosacea received 15 IU pra-BoNTA to one cheek and normal saline to the other. Significant improvement in erythema, skin elasticity, and hydration was observed on the pra-BoNTA-treated side 2 months after treatment [110]. In a double-blind placebo-controlled RCT performed by Dayan et al. [111], nine patients with rosacea received either 10 IU inco-BoNTA per cheek or saline. Sustained improvement in rosacea was observed in the inco-BoNTA-treated group 4 weeks after treatment. After 16 weeks, both groups received treatment with inco-BoNTA and exhibited improved rosacea and patient satisfaction [111]. Odo et al. [112] conducted an RCT investigating the efficacy of abo-BoNTA in 60 menopausal women with hot flushes. Patients received 500 IU abo-BoNTA or normal saline placed at 40 injection sites across the face, neck, chest, and scalp. Abo-BoNTA-treated patients reported a decrease in severity and frequency of sweating, hot flushes, and night sweats for 2 months after treatment [112]. Park et al. [113] performed a prospective study of 20 patients with rosacea who received 10 IU BoNTA per cheek. Diminished erythema severity and telangiectasias as well as improved patient satisfaction were sustained 2 months after treatment [113]. In another prospective study, 24 patients with facial flushing received 15 IU BoNTA per cheek and exhibited significant improvement in facial flushing 2 months after treatment [114]. Geddoa et al. [115] investigated the effects of BoNTA on idiopathic neck and chest flushing; 22 patients received 1–2 IU aliquots of a maximum dose of 100 IU BoNTA at the neck and chest wall. Of these patients, 20 experienced immediate improvement after a single treatment, and two attained similar resolution following retreatment. At the 4-week follow-up, all patients reported significant improvement [115]. Bloom et al. [116] performed another prospective study in which 15 patients with rosacea received a single treatment with 15–45 IU abo-BoNTA to the forehead, nose, cheeks, and chin. Significant improvement in facial erythema was observed 3 months after treatment [116].

4.4 Gastrocnemius Muscle Hypertrophy

Sustained improvement of gastrocnemius muscle hypertrophy for improved leg contour was reported for 3–6 months following treatment with 32–100 IU BoNTA/calf, 80–200 pra-BoNTA/calf, and 300–360 abo-BoNTA/calf [117–123]. In a prospective randomized comparative study of 40 patients with gastrocnemius muscle hypertrophy, Suh et al. [117] observed improved leg contour in all patients, with similar efficacy following treatments with either 80 or 100 IU pra-BoNTA injected in varying techniques in the medial and lateral aspects of each calf. A prospective double-blind comparative study of 22 patients reported that 100 IU BoNTA and 100 IU pra-BoNTA per calf were equally effective for the improvement of lower leg contour 6 months after treatment [118].

4.5 Gummy Smile

Gummy smile (GS) results from excessive exhibition of gingival tissue of the maxilla while smiling. Mazzuco and Hexsel [124] identified four types of GS: anterior, posterior, mixed, and asymmetric. Anterior GS is defined as >3 mm gum exposure between canine teeth. Treatment for anterior GS includes injections of 2.5–5 IU abo-BoNTA to the nasolabial fold 1 cm inferolateral to the nasal ala to relax the levator labii superioris alaeque nasi. Posterior GS involves >3 mm gum exposure posterior to canines. Treatment for posterior GS includes injections of 2.5 IU abo-BoNTA at two points in the malar region to relax zygomatic muscles. Mixed GS is defined as >3 mm gum exposure in the anterior and posterior regions. Treatment for mixed GS includes injections of 2.5 IU abo-BoNTA at three points in the malar and nasal ala regions. Asymmetric GS involves >3 mm gum exposure unilaterally. Treatment for asymmetric GS includes injections of 2.5 IU abo-BoNTA at two points in the malar region on the hyperkinetic side [124]. A case report of a woman with mixed GS treated with 2 IU BoNTA injected into two points at each levator labii superioris and 5 IU BoNTA injected into each zygomaticus minor (18 IU total) described a significant decrease in gingival exposure 5 months after treatment [125].

4.6 Leonine Facies

Pachydermoperiostosis (PDP) is a rare genetic disorder resulting in pachydermia, digital clubbing, and periostosis. Leonine facies caused by pachydermia is especially debilitating to patients. Three patients with PDP-associated leonine facies received 70–80 IU BoNTA infiltrated at 15 injection sites to the procerus, corrugators, and brow. All patients demonstrated a fair/excellent response within 6 weeks [126].

4.7 Masseter Muscle Hypertrophy

Masseter muscle hypertrophy presents a cosmetic concern for many patients. Several studies described the efficacy of BoNTA, inco-BoNTA, pra-BoNTA, and abo-BoNTA for the treatment of masseter muscle hypertrophy [127–138]. An RCT investigated how to increase the duration before masseter rehypertrophy following treatment with BoNTA. A total of 98 patients received 35 IU BoNTA to each masseter. Patients who were instructed to intentionally strengthen their masticatory muscles during the denervated atrophic stage exhibited significantly prolonged durations of efficacy compared with control patients [127]. In a 4-year follow-up study, 50 Asian Indian patients with masseter muscle hypertrophy received two to three treatments with 30 IU BoNTA to each masseter at 3- to 4-month intervals. All patients exhibited improved facial contour that was maintained for 4 years [128]. In a case-controlled study, 220 patients with masseter muscle hypertrophy received 20–40 IU BoNTA per masseter and exhibited decreased masseter thickness 3 months after treatment. The overall patient satisfaction rate with improved facial contour was 95.9% [129]. In a split-face RCT, 56 patients received 25 IU BoNTA to one masseter and 25 IU inco-BoNTA to the other. Masseter volume reduction was observed on both sides with no significant difference between sides [133]. Similarly, a prospective study of 35 patients found that efficacy of ona-BoNTA and pra-BoNTA was comparable for masseter reduction [134]. In a prospective randomized study, 30 patients received 40 IU inco-BoNTA using either a single or a multiple injection technique. Significant masseter muscle reduction was observed in both groups, with no difference between injection techniques [135]. A retrospective study of 383 patients reported the efficacy of abo-BoNTA for the treatment of masseter muscle hypertrophy, with 93% patient satisfaction [137].

4.8 Oily Skin and Enlarged Pores

Oily skin is associated with increased sebum production and enlarged pores. A split-face controlled study by Sayed et al. [139] reported the efficacy of intradermal injections of BoNTA for decreasing sebum production and pore size 4 months after treatment [139]. In a prospective study by Rose and Goldberg [141], 25 patients with oily skin received 3–5 IU aliquots of 30–45 IU abo-BoNTA placed at ten injection sites at the brow. An average of 80% reduction in sebum production as well as improved patient satisfaction was observed [141]. A prospective double-blind randomized study investigated the dose-comparative effect of BoNTA on sebum production in patients who received intramuscular injections of BoNTA for facial rejuvenation, with 42 patients receiving either 10 or 20 IU BoNTA placed at five injection

sites in the frontalis muscle. Both groups demonstrated a significant decrease in sebum production at injection sites but increased compensatory sebum production at a radius 2.5 cm from injection sites. Higher BoNTA dose did not correlate with increased efficacy or duration [140].

4.9 Pectoral Muscle Contraction

A case report described a female patient 6 months after breast augmentation who experienced tethering of inferior breasts upon contraction. BoNTA injected into the pectoralis major resulted in complete resolution of tethering [142]. Another case report described the efficacy of BoNTA for treating pectoral spasm following implant insertion [143].

4.10 Salivary Gland Hypertrophy

Bae et al. [144] described two patients with salivary gland hypertrophy that was successfully treated with BoNTA injections. The first patient received 30 IU BoNTA injected percutaneously into the left parotid gland. The second patient, with hypertrophic parotid and submandibular glands, received three treatments with 28–38 IU BoNTA to each parotid gland and 20 IU BoNTA to each submandibular gland at 2-month intervals [144]. Another case series reported improvement in posterior cheek enlargement in two patients with HIV following treatment with BoNTA injected into each parotid gland and masseter muscle [145].

4.11 Scar Prevention

Hypertrophic scars and keloids are aberrant responses to the wound healing process caused by excess collagen deposition and dysregulated growth. The suggested role of BoNTA in wound healing as well as scar prevention and treatment is threefold: BoNTA blocks acetylcholine release and chemoimmobilizes surrounding musculature, thereby minimizing repetitive tension around wound edges. BoNTA acts on the cutaneous vasculature and mitigates the inflammatory phase of wound healing. BoNTA has been reported to directly suppress fibroblast proliferation and modulate transforming growth factor (TGF)-β1 expression [169]. Several reports have demonstrated the efficacy of BoNTA injections for prevention of hypertrophic scars from traumatic wounds and surgical incision sites.

4.11.1 Facial Wounds

In a split-scar RCT, Hu et al. [146] investigated the efficacy of BoNTA for preventing facial scars in 16 patients following facial reconstructive surgery. Immediately after wound closure, scar halves received BoNTA or saline injected 5 mm from the scar periphery. BoNTA-treated scar halves exhibited significantly decreased scar height and width 6 months after treatment. No significant difference in scar pigmentation, pliability, or vascularity was observed between the two halves [146]. Lee et al. [147] observed improved scar cosmesis in patients with forehead lacerations treated with pra-BoNTA injections within 5 days of wound closure compared with patients who received no treatment [147]. In an RCT of 24 patients with facial wounds who received BoNTA within 72 h postoperatively, improvement in scar cosmesis based on photographic analysis was significant, but no significant difference was observed for other score scales [148]. In an RCT by Gassner et al. [149], 31 patients received 15–45 IU or saline to forehead lacerations within 24 h of wound closure. The BoNTA group exhibited significant improvement in scar cosmesis 6 months after treatment [149].

4.11.2 Post-Epicanthoplasty

In a split-face RCT, 30 patients who had undergone epicanthoplasty received 5 IU BoNTA injected subcutaneously to the medial canthi on one side and saline to the other 6–7 days postoperatively. Significant scar height reduction and increased pliability was observed in the BoNTA-treated sides 3–6 months after treatment [150].

4.11.3 Post-Cheiloplasty

Chang et al. [151] conducted an RCT of 3-month-old infants with unilateral cleft lip. Immediately after wound closure post-cheiloplasty, 59 infants received injections of 1 IU BoNTA/kg or saline into the orbicularis oris. The BoNTA group exhibited significantly improved subjective scar cosmesis and decreased scar width compared with the control group 6 months after treatment. However, no significant difference in pigmentation, vascularity, pliability, or height was observed between groups [151]. In an RCT, patients aged 4–24 months with unilateral or bilateral cleft lip and palate received 8 IU BoNTA (maximum 2 IU/kg) or saline injected into the orbicularis oris muscle 7–10 days prior to cheiloplasty. BoNTA-treated patients displayed decreased scar width and improved cosmesis 6 months postoperatively [152]. Chang et al. [153] conducted another RCT in 58 adults following cleft lip scar revision surgery. Patients received 15 IU BoNTA or saline placed into the orbicularis oris muscle 5 mm from the wound periphery immediately after closure. The BoNTA group demonstrated significant improvement in scar pigmentation, vascularity, and pliability as well as decreased scar height and width compared with the control group 6 months after treatment [153].

4.11.4 Post-Thyroidectomy

In an RCT, 15 patients who had undergone thyroidectomy received injections of either 20–65 IU BoNTA or saline to scar halves within 10 days of surgery. The BoNTA-treated halves exhibited significantly improved cosmesis 6 months after treatment [154]. An RCT by An et al. [155] investigated the appropriate timing of pra-BoNTA injections for thyroidectomy scar prevention. Patients received 5 IU aliquots of a maximum of 60 IU pra-BoNTA to one side of the scar immediately postoperatively and to the contralateral side 2 weeks postoperatively. The operation-day injection sides exhibited significantly improved erythema, skin elasticity, and incision line cosmesis compared with the 2-week postoperative injection sides. No difference in scar width, height, melanin index, or scar friction was observed between injection sides [155].

Despite the reported efficacy of BoNTA for scar prevention, a few reports have described no significant effect of BoNTA injections on scar prevention compared with saline placebo. In an RCT by Phillips et al. [156], 40 patients received 15 IU BoNTA or saline placebo to contralateral scar halves post-thyroidectomy. No difference in scar cosmesis was observed between scar halves. However, patients with a history of severe scarring exhibited significantly reduced scarring on the BoNTA-treated side 6 months postoperatively [156]. The results published by Phillips et al. [156] have attracted criticism of the patient categorization, scar assessment modalities, and role of ethnicity and Fitzpatrick skin type in scar prevention [170, 171].

4.11.5 Post-Sternotomy

In an RCT, 17 patients received 5 IU aliquots of a total 50–70 IU BoNTA or normal saline at upper and lower scar halves within 14 days post-sternotomy. The BoNTA-treated halves exhibited significantly improved pigmentation, vascularity, pliability, scar height, scar width, and patient subjective satisfaction 6 months after treatment [157].

4.12 Scar Treatment

4.12.1 Keloids

Shaarawy et al. [158] conducted an RCT of BoNTA versus intralesional corticosteroid injections for the treatment of keloids in 24 patients: 12 patients received three treatments with 5 IU BoNTA/cm^3 of keloid at 8-week intervals or until complete remission, and 12 patients received six treatments with corticosteroid injections at monthly intervals or until complete remission. Significant decreases in volume, elevation, and erythema were observed in both groups, with little difference between groups 7 months after treatment. While both groups demonstrated significant softening of keloids compared with baseline, the steroid group demonstrated significantly greater softening compared with the BoNTA group. However, subjective symptoms of itching, pain, and tenderness significantly improved in the BoNTA group compared with the corticosteroid group. The BoNTA group also did not exhibit the injection pain or postinjection skin atrophy and telangiectasia that was reported in the steroid group [158]. In an RCT, Pruksapong et al. [159] compared the efficacy of BoNTA and intralesional corticosteroid injections for the prevention of keloid reoccurrence following surgical excision: 25 patients underwent keloid excision and then received either a single treatment with 12–24 IU BoNTA (1.5 IU/cm of keloid) or three treatments of corticosteroid injections at monthly intervals. Both treatment groups exhibited significant improvement in scar pigmentation, height, vascularity, and pliability compared with baseline. Whereas the BoNTA group exhibited significant improvement over the steroid group 1 and 3 months after treatment, the steroid group exhibited significant improvement over the BoNTA group 6 months after treatment [159]. In a prospective study by Zhibo and Miaobo [160], 12 patients with keloids received 70–140 IU BoNTA at 3-month intervals for a maximum of 9 months. Regression and flattening of keloids and high patient satisfaction were observed in all patients and sustained without reoccurrence 12 months after the initial treatment [160]. A case series of 12 patients reported complete flattening of keloid scars after multiple treatments of BoNTA over an average period of 18 months [162]. In a case report of a woman with a painful chest keloid treated with 100 IU BoNTA, pain was reduced 5 weeks after treatment, but no change in pruritus or physical appearance of the keloid was noted [163].

In a prospective study by Gauglitz et al. [161], four patients with keloids received three treatments with 70–140 IU abo-BoNTA at 2-month intervals. At 3 months after the final treatment, no significant difference in appearance, morphology, or size of keloids was observed. Additionally, no differences in TGF-β1 of keloid fibroblasts were found in BoNTA-treated specimens [161]. The findings of this study are inconsistent with those of a recent systematic review and meta-analysis that demonstrated that BoNTA was more effective than intralesional corticosteroid or placebo for treatment of hypertrophic scars and keloids. Patients who received BoNTA reported a lower incidence and severity of pain than did patients who received intralesional corticosteroid. BoNTA-treated scars showed statistically significant improvement in melanin pigmentation, scar height, vascularity, pliability, and scar width [172].

4.12.2 Hypertrophic Scars

In a prospective study by Xiao et al. [165], 19 patients with hypertrophic scars received 2.5 IU BoNTA/cm^3 of a single hypertrophic lesion at the face, earlobe, neck, chest, back, or buttock. Total BoNTA doses ranged from 2 to 87.5 IU. Patients received three treatments at monthly intervals. Significant reductions in erythema, pliability, and pruritus were observed 6 months after treatment [165]. In a similar prospective study of 20 patients with hypertrophic scars on the face, neck, chest, shoulder, and extremities, significant reductions in erythema, pliability, and pruritus were observed 6 months after three treatments with 2.5 IU BoNTA/cm^3 for a maximum dose of 100 IU BoNTA at monthly intervals [164].

4.13 Temporal Muscle Hypertrophy

In a prospective study, 20 patients with temporal muscle hypertrophy received 25 IU BoNTA placed at five injection points at the temporalis. Reduction in temporal muscle thickness and upper face circumference was sustained for 5–6 months after treatment [166]. A patient with temporal and masseter muscle hypertrophy sustained marked muscle atrophy for 13 months following three treatments with 100 IU abo-BoNTA per temporal muscle [138].

4.14 Trapezius Muscle Hypertrophy

Improved neck and shoulder contour has been reported following treatment with BoNTA injections. In a prospective study, 30 female patients received 7–10 IU aliquots of a total 50 IU BoNTA placed at five to seven injection sites into each trapezius muscle. Improvement was sustained for 6–10 months after treatment [167]. A case series of two patients treated with 50 IU pra-BoNTA described similar results [168].

5 Hair Growth

Table 5 lists the results of studies in hair growth with botulinum toxin type A.

5.1 Androgenetic Alopecia

In a prospective study, 50 male patients with androgenetic alopecia received 5 IU aliquots of a total 150 IU BoNTA placed at 30 injection sites into the frontalis, temporalis, occipitalis, and preauricular muscles. In total, 40 patients completed the study and demonstrated a significant increase in hair counts 4 months after treatment [173]. Singh et al. [174] observed similar results in another pilot study of ten male patients with androgenetic alopecia [174]. A prospective study by Zhang et al. [175] investigated the efficacy of low-dose BoNTA for the treatment of androgenetic alopecia in male Chinese patients. A total of 24 patients received 50 IU BoNTA placed at 30 injection sites in the frontalis, temporalis, occipitalis, and preauricular muscles; 11 patients exhibited a $>10\%$ increase in hair count 6 months after treatment [175].

5.2 Cephalalgic Alopecia

Cephalalgic alopecia is a rare condition involving recurring episodes of severe head and neck pain accompanied by hair loss in symptomatic areas. Cutrer and Pittelkow [176] successfully treated a 34-year-old woman with cephalalgic

Table 5 Hair growth with botulinum toxin type A

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration (months)	Results
Androgenetic alopecia	PS (IV) [173, 174]	150 IU (frontalis/temporalis/occipitalis/preauricular muscles)	6–12	SI
	PS (IV) [175]	50 IU (frontalis/temporalis/occipitalis/preauricular muscles)	6	Minor improvement in less than half of pts
Cephalalgic alopecia	CRep (IV) [176, 177]	100 IU (procerus/ corrugator/frontalis/ temporalis/ splenius/capitis/occipitalis/trapezius muscles)	2	CR
Folliculitis decalvans	CS (IV) [178]	80–150 IU (scalp)	6–8	Hair growth in three of four pts
Radiation-induced alopecia	CRep (IV) [179]	150 IU (frontalis/temporalis/periauricular/occipitalis muscles)	3–12	SI

BoNTA botulinum toxin type A, *CR* complete response, *CRep* case report, *CS* case series, *PS* prospective study, *pts* patients, *SI* sustained improvement

alopecia with 100 IU BoNTA. After retreatment 3 months later, she exhibited significant hair regrowth and pain diminution sustained for 2 months [176]. Another case report described improvement following similar treatment parameters [177]. Cutrer et al. [180] later evaluated scalp biopsies from the same patient. The untreated scalp biopsy specimens exhibited peribulbar lymphocytic infiltrate as well as decreased density of SP-positive and CGRP-positive nerve fibers in the epidermal neural plexus. However, BoNTA-treated specimens displayed increases in nerves containing SP and CGRP [180].

5.3 Folliculitis Decalvans

In a case series, four male patients with folliculitis decalvans exhibited improvement following treatment with 2.5 IU aliquots of a total of 80–150 IU BoNTA injected at 0.5 cm intervals into the scalp. All patients exhibited reduced secretion. Three patients noted hair growth. The two most severe cases responded most favorably to treatment [178].

5.4 Radiation-Induced Alopecia

A 65-year-old female with radiation-induced alopecia at the frontoparietal scalp received of a total of 150 IU BoNTA placed at 30 injection sites. She received four treatments at 3-month intervals and exhibited increased hair growth and improved hair density and thickness 12 months after the initial treatment [179].

6 Miscellaneous

A list of miscellaneous conditions treated with botulinum toxin type A is provided in Table 6.

6.1 Apocrine Hidrocystomas

Apocrine hidrocystomas are rare benign cystic lesions. A 29-year-old man with multiple apocrine hidrocystomas at the glabella, brow, and temple regions received perilesional and intralesional injections of 2 IU aliquots of a total 20 IU BoNTA to the glabella. He exhibited flattening of lesions sustained until retreatment 8 months later, and improvement was sustained for 2 years [181].

6.2 Aquagenic Keratoderma

Aquagenic keratoderma (AK) is a transient condition distinguished by thick pebbling and wrinkling of the skin following aquatic immersion. BoNTA injections are an effective therapeutic tool for alleviating the symptomatic pain, pruritus, and tightness in patients with AK with and without associated hyperhidrosis. Several case reports have described complete remission of pain and pruritus for 2–6 months following treatment with 50–100 IU BoNTA per palm [182–185].

6.3 Darier's Disease

Several case reports have described the efficacy of BoNTA for the treatment of Darier's disease. A 59-year-old woman with Darier's disease received 50 IU BoNTA per submammary area and exhibited sweat reduction and thereby diminution of pain, burning, itching, tightness, and malodor for 4 months after treatment [186]. Another patient with Darier's disease and concomitant intertrigo exhibited sustained improvement after receiving 40 IU BoNTA per inguinal fold and 20 IU BoNTA per anal fold [187]. A man with Darier's disease received five treatments with 200 IU BoNTA at the intergluteal fold and sustained remission of malodorous and pruritic vegetative lesions for 6 months [188].

6.4 Eccrine Hidrocystomas

Eccrine hidrocystomas are benign cystic lesions of the eccrine glands. Several studies have reported success with intradermal injections of BoNTA for treating multiple eccrine hidrocystomas without the risk of scarring [189–193]. In a prospective study, 18 patients with facial eccrine hidrocystomas received one to two treatments with 6–12 IU abo-BoNTA and exhibited flattening of lesions for a duration of 5–7 months [189]. In another prospective study, 20 patients with multiple eccrine hidrocystomas received 1.5 IU abo-BoNTA injected at the base of each lesion. More than 75% of eccrine hidrocystoma lesions cleared in all patients after 7 days, and improvement was sustained for 2–5 months [190]. A case report indicated that electrocautery was superior to BoNTA for the treatment of periorbital eccrine hidrocystomas despite the risk of postinflammatory hyperpigmentation associated with electrocautery [193].

6.5 Epidermolysis Bullosa Simplex

Epidermolysis bullosa simplex (EBS) is a rare genodermatosis characterized by blistering at the extremities following frictional trauma. In a retrospective study, five of six patients with EBS who received abo-BoNTA reported improvement in callosities, blisters, and pain [194]. In a case study of a woman with EBS, Weber–Cockayne type, investigators who were blinded to treatment administered plantar injections of 100 IU BoNTA to one foot and normal saline to the other. She exhibited a significant decrease in number of blisters on the BoNTA-treated foot 3 months after treatment [195].

Table 6 Miscellaneous treatment with botulinum toxin type A

Condition	Study type (level of evidence) [2]	BoNTA dose (location)	Duration[a]	Results
Apocrine hidrocystomas	CRep (IV) [181]	20 IU (glabella)	8–24	CR
Aquagenic keratoderma	CRep (IV) [182, 183]	50 IU/palm	5–6	CR
	CRep (IV) [184, 185]	100 IU/palm	≥2	CR
Darier's disease	CRep (IV) [186]	50 IU/submammary area	4	CR
	CRep (IV) [187]	40 IU/inguinal fold; 20 IU/anal fold	3	CR
	CRep (IV) [188]	200 IU (intergluteal fold)	6	CR
Eccrine hidrocystomas	PS (IV) [189]	6–12 IU abo-BoNTA (facial hidrocystomas)	5–7	CR
	PS (IV) [190]	1.5 IU abo-BoNTA/lesion	2–5	CR
	CRep (IV) [191]	10 IU (upper eyelids/glabella/nose/cheeks/upper lip)	6	CR
	CRep (IV) [192]	60 IU (central facial lesions)	4	CR
	CRep (IV) [193]	2.5 IU (medial canthus)	2	Improvement until reoccurrence
		Electrocautery (lateral canthus)	≥2	PIH; CR
Epidermolysis bullosa simplex	RS (IV) [194]	85–350 IU abo-BoNTA/foot	3–4	SI in five of six patients
	CRep (IV) [195]	100 IU/foot vs. normal saline	3	SI in BoNTA foot
Hailey–Hailey disease	CS (IV) [196, 197]; CRep (IV) [198–200]	50–125 IU/axilla	3–6	SI
	CS (IV) [196, 197], CRep (IV) [198, 201]	50–125 IU/inguinal fold	4–6	SI
	CS (IV) [196]	2.5 IU/cm^2 of plaque (noninterstriginous sites)	4	SI
	CS (IV) [202]	500 IU abo-BoNTA (neck, submammary, axillae, abdomen, groin)	1–34	Partial remission–complete remission
	CRep (IV) [203]	100 IU (intergluteal cleft)	3–6	SI
	CRep (IV) [204]	100 IU BoNTA (submammary) vs. BoNTA + erbium:YAG vs. BoNTA + dermabrasion	12	Complete remission in all groups
Linear IgA bullous dermatosis	CRep (IV) [205]	50 IU/axilla	6	SI
Plaque psoriasis	RCT (II) [206]	36 IU abo-BoNTA (per 1–2 plaques)	8 wk	No clinical efficacy
	PS (IV) [207]	25–98 IU (single plaque)	10 wk	Significant clinical improvement
	CRep (IV) [208]	30 IU abo-BoNTA (single plaque)	7	Complete remission
Pachyonychia congenita	RS (IV) [194, 209], CS (IV) [210]	200–500 IU abo-BoNTA/foot	2–12	SI–CR
	RS (IV) [209], CS (IV) [211]	100–200 IU/foot	3–6	SI–CR
	CS (IV) [211]	50 IU/palm	5–6	SI

abo-BoNTA abobotulinumtoxin A, *BoNTA* botulinum toxin type A, *CR* complete response, *CRep* case report, *CS* case series, *IgA* immunoglobulin A, *PIH* post-inflammatory hyperpigmentation, *PS* prospective study, *RCT* randomized controlled trial, *RS* retrospective study, *SI* sustained improvement, *wk* weeks

[a]Duration indicated in months unless otherwise indicated

6.6 Hailey–Hailey Disease (Familial Benign Pemphigus)

Hailey–Hailey disease (HHD) is an autosomal dominant bullous disease distinguished by erythematous plaques and erosions at the intertriginous regions. Several case studies and reports have described the efficacy of BoNTA and abo-BoNTA as an adjuvant treatment for patients with HHD [196–204]. In a side-by-side comparison case report, a patient with HHD received intracutaneous injections of BoNTA to bilateral submammary regions. A 25 cm^2 area on each side was then additionally treated with erbium:YAG laser or dermabrasion. The areas treated with BoNTA alone exhibited complete remission comparable to the areas treated with the combined BoNTA and ablative treatments [204].

6.7 Linear Immunoglobulin A Bullous Dermatosis

A single case report described the efficacy of BoNTA for the treatment of a linear immunoglobulin A (IgA) bullous dermatosis. A 17-year-old patient with linear IgA bullous dermatosis received 50 IU BoNTA to one axilla. Clinical improvement and high patient satisfaction after 3 weeks prompted treatment of the other axilla. The patient experienced remission until retreatment 6 months later [205].

6.8 Plaque Psoriasis

Todberg et al. [206] conducted an RCT in eight patients who received a single treatment with 36 IU abo-BoNTA spread across one to two plaques. The trial was suspended after failure of preliminary statistical clinical efficacy after 8 weeks. It is important to note that only eight of the planned 20 subjects were analyzed and not all analyses were performed prior to trial suspension [206]. However, a prospective study of eight patients with plaque psoriasis who received 25–98 IU BoNTA (average 53 IU) per plaque described statistically significant clinical improvement 8 weeks after treatment [207]. An earlier case report described a patient with recalcitrant plaque psoriasis who received 30 IU abo-BoNTA to a single plaque and exhibited complete remission for 7 months [208].

6.9 Pachyonychia Congenita

Pachyonychia congenita (PC) is a rare genodermatosis characterized by hypertrophic nails and plantar keratoderma. In a retrospective study and several case series, patients with PC who received treatment with palmar and plantar injections of BoNTA and abo-BoNTA exhibited improvement in painful blisters and callosities sustained for 2–12 months [194, 209–211]. Drastic reductions in plantar pain following BoNTA and abo-BoNTA treatments enabled two wheelchair-bound patients to walk again [210, 211].

7 Side Effects and Limitations

Despite its high safety profile and widespread multidisciplinary use, BoNTA does have side effects and limitations. A primary limitation of BoNTA is the high cost of treatment, especially since many of the off-label uses of BoNTA are for chronic diseases requiring multiple treatments at regular intervals. Side effects reported with the alternative uses of BoNTA are often transient and commonly resolve within 2 days to 12 weeks (Table 7) [215]. The pain of injections, especially at the palmoplantar sites, discourages patient adherence to BoNTA therapy. When treating bruxism, doses of < 100 IU BoNTA per masseter are recommended to prevent adverse side effects such as change in bite force, speech

Table 7 Reported side effects following off-label uses of botulinum toxin type A

Body region	Reported side effects
Upper/midface	Atrophy [212], decreased frontalis tone [141], facial muscle paralysis [113], frontalis muscle weakness [14], injection site pain [14, 17], lagophthalmos [190], ptosis (eyebrow/eyelid) [16, 126]
Lower face	Atrophy/sunken cheeks [132, 212, 213], asymmetric oral commissure [124, 152, 190], bruising [135, 213], downturn smile [124], edema [135], facial asymmetry [124, 131], headache [130, 213], hematoma [135], injection site pain [130, 135, 138], jowling [213], masticatory function impairment [124, 131, 132, 213, 214], paradoxical bulging [213], smile impairment [60, 124, 192, 213], speech impairment [124, 131], upper lip drooping [16]
Neck/chest/back	Bruising [168], burning sensation [107], injection site pain [155, 157, 168], shoulder soreness [167], shoulder movement impairment [167]
Palms/soles	Bruising [209], edema [209], gait instability [47], palmar injection site pain [37, 40, 42, 84, 86, 90], palmar weakness [34, 36, 37, 43, 68, 85–88, 90], plantar injection site pain [40, 47, 209], plantar weakness [46, 47], sensory disturbance [47], thenar atrophy [46]
Lower legs	Bruising [120–122], muscle cramp [118, 119, 122], muscle fatigue/weakness [122], myalgia [118, 122], injection site pain/tenderness [120, 121]
Genitalia	Burning sensation [101], injection site pain [25, 51, 99, 101], perianal thrombosis/abscess [105], transient fecal incontinence [52, 54, 105]

disturbance, and muscle weakness [57–59, 61]. Lower leg weakness and fatigue while standing were reported in a patient receiving high doses of abo-BoNTA (> 300 IU/calf) for the treatment of gastrocnemius muscle hypertrophy [122]. Proper knowledge of target anatomy and injector skill are paramount for preventing potential adverse reactions.

Muscular atrophy can be both a desired and an undesired clinical outcome of BoNTA injections and both temporary and reversible [212]. Studies have reported sunken temporal fossa and cheeks. Muscular atrophy and concomitant intramuscular fat deposition were observed 3 months after repeated treatments with high-dose BoNTA [216]. Intramuscular lipid deposition might lead clinicians to underestimate the extent of BoNTA-induced atrophy [217]. More studies are needed to elucidate this issue.

Immunoresistance and tachyphylaxis present another concern. Although the development of neutralizing antibodies is uncommon with current formulations of BoNTA, reports of immunoresistance have been associated with shorter treatment intervals, booster injections, higher doses, and increased levels of antigenic protein as well as differences in the formulation, manufacturing, and storage of BoNTA. As a consequence, administration of proper doses at a minimum of 3-month treatment intervals is recommended [218]. Despite the safety profile of BoNTA, anaphylaxis and anaphylactoid reactions remain a concern. Li et al. [219] reported fatal anaphylaxis in a 43-year-old patient treated with BoNTA mixed with lidocaine. To avoid interference with pharmacokinetics, BoNTA should never be mixed with local anesthetics. Moon et al. [220] reported a case of anaphylaxis in a 35-year-old woman who received regular treatments of BoNTA for masseter muscle hypertrophy. In response to this report of anaphylaxis, Pickett [221] speculated the possible unintentional administration of a counterfeit or unlicensed BoNTA product. Serious adverse effects have been reported with counterfeit and unlicensed BoNTA products, and their use poses a serious risk to patients [222].

8 Conclusion

BoNTA has a high efficacy and safety profile so has become an effective multidisciplinary therapeutic tool. While new trends in and reports of BoNTA applications for the treatment of a large number of dermatologic diseases are encouraging, much of the literature consists of single case reports and uncontrolled prospective studies with small sample sizes and qualitative outcome measures. Larger RCTs are needed to elucidate the standardization of dose regimens and injection techniques for safe and effective use of BoNTA for off-label indications. No doubt, the vast therapeutic potential of BoNTA will continue to grow.

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