The Use of Botulinum Toxin in Pain Management: Basic Science and Clinical Applications

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Summary: Pain is an unpleasant experience resulting from either tissue damage or insults to the somatosensory system. Approaches to pain management evolve as we better understand both pain pathways and the tools available to interrupt these. The interest surrounding botulinum neurotoxin as a chemodenervating agent has expanded to include its potential applications in painful pathologies, both within and beyond the confines of plastic surgery. In this article, the authors discuss botulinum neurotoxin's mechanism of action as it pertains to both muscular paralysis and its interplay in the modulation of proinflammatory pain mediators. In addition, the authors review evidence supporting the use of botulinum neurotoxin in common painful conditions, in order to prepare the readership to aptly provide their patients with evidence-based recommendations. After reading this article, the participant should be able to discuss both mechanism of action and common applications of botulinum neurotoxin in painful conditions. (*Plast. Reconstr. Surg.* 145: 629e, 2020.)

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."[1] Pain can be classified as neuropathic, nociceptive, or mixed. Nociceptive pain results from tissue damage.[2] Neuropathic pain results from disturbance or damage to the somatosensory system, either peripheral or central, culminating in allodynia, hyperalgesia, or dysesthesia.

Peripheral neuropathic pain is believed to result from peripheral nerve damage leading to nerve ending irritation and higher concentrations of neurotransmitters and pain modulators, such as substance P, glutamate, and calcitonin gene-related peptide (CGRP). Repetitive nerve ending damage results in local inflammation, lowered nociceptive threshold to stimuli, and ultimately in continued pain.

Botulinum neurotoxin type A (BoNTA) received its first U.S. Food and Drug Administration approval in 1989 for the treatment of strabismus and blepharospasm, and since that time, the approved indications for Botox (Allergan, Irvine, Calif.) have grown to include overactive bladder, urinary incontinence, extremity spasticity, cervical dystonia, severe axillary hyperhidrosis, blepharospasm, strabismus, chronic migraine headache, and the temporary improvement of glabellar, lateral canthal, and forehead rhytides.[3] In addition to these indications, the reported uses of BoNTA have expanded to include the treatment of multiple painful conditions, commonly representing an off-label use (Table 1). In many avenues of medicine, the application of botulinum neurotoxin and its chemodenervating effects are well established. However, the exact mechanisms in its application to painful conditions are commonly only partially understood and still being elucidated.

BOTULINUM TOXIN PAIN MECHANISM OF ACTION

Botulinum neurotoxin is naturally produced by the anaerobic, spore-forming bacteria *Clostridium*.[4,5] The toxin causes flaccid paralysis at peripheral skeletal and autonomic nerve terminals by entering the cytosol of the nerve terminals and

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Table 1. Treatment Indications for Botulinum Neurotoxin

Painful Condition	GRADE	Level of Evidence	Key Findings	Weakness/Limits
Migraine headache	High	Mathew et al.,[25] I Dodick et al.,[26] I	Reduced HA frequency, severity, and acute medication	High placebo effect, difficulty blinding long term
		Aurora et al.,[27] I	Reduced HA frequency, MH days, and HA hours	Some outcome measures not powered sufficiently, no active comparator for MH prophylaxis at time of study
		Janis et al.,[31] III	Reduced MHI, HA days/month, and MH severity	Small sample, unmatched baseline MH characteristics
Trigeminal neuralgia	Moderate	Shehata et al.,[45] II	Reduced pain and acute weekly medication use	Blinded only to participant, small sample, unclear if matched cohorts
		Xia et al.,[46] II	Reduced pain, sleep interference, anxiety/depression scores	Only a treatment cohort, no comparative outcomes
		Zhang et al.,[47] II	Reduced pain	Small cohort size, power not documented
		Meng et al.,[48] I	Reduced pain up to 24 weeks	Multiple neuralgia etiologies, relatively small sample size, heterogeneity of results compared
Postherpetic neuralgia	Moderate	Xiao et al.,[49] II	Improved pain and sleep, reduced opioid use	Participant opioid use not controlled, dose-response unknown due to varied injection technique
		Apalla et al.,[50] II	Improved pain and sleep	Small sample, yet powered, single injection study limits applicability to patients with sustained pain
Urologic/pelvic floor	Moderate	Wang et al.,[54] I	Improved pelvic pain, interstitial cystitis, and decreased daytime urination	Limited studies with small sample sizes and poorly defined methods, variability in BoNTA dose across studies, short follow-up among studies in setting of chronic medical condition
		Abbott et al.,[55] I	Reduction in dyspareunia and nonmenstrual pelvic pain	Potential psychosocial confounding in vulnerable patient population, larger placebo effect than expected, concern for type II error
		Morrissey et al.,[56] II	Improvement in dyspareunia and quality-of-life scores	Small sample size, lack of control arm, concern for interobserver error, pudendal nerve block at time of administration represents possible confounder
Abdominal wall	Low	Zendajas et al.,[41] III	Improved pain and lower morphine equivalent use	Small sample size, not matched on hernia size, not controlled for nonnarcotic analgesia
Vasospastic hand	Low	Neumeister et al.,[39] III	Pain resolution, healed ulcerations, increased perfusion	Retrospective, uncontrolled case series, no placebo
		Neumeister,[38] III	Reduced pain, improved tissue perfusion	Multiple possible confounders
		Motegi et al.,[37] V	Decreased relative Raynaud's scores, improved pain and skin temperature, healed ulceration	Case series, small sample, lack of control, varied severity of Raynaud's phenomenon
		Fregene et al.,[40] III	Improved pain, transcutaneous oxygenation, healed ulceration	Retrospective, without control, varied injection sites
Diabetic neuropathy	Low	Yuan et al.,[52] II	Improved pain	Small sample size, unknown if powered
		Ghasemi et al.,[53] II	Reduced pain and other peripheral neuropathy symptoms	Small sample, unknown if powered, short-term, 3-week results reported
Phantom limb	Very low	Jin et al.,[43] V	Reduced pain and medication use	Case report ($n = 3$), varied BoNTA dose
		Wu et al.,[44] II	Improved residual limb pain, but not phantom limb pain from baseline, no difference between treatment cohorts	Small sample size, unmatched baseline pain

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HA, headache; MH, migraine headache; MHI, Migraine Headache Index.

cleaving SNAP-25 SNARE proteins, thereby inhibiting acetylcholine release.[6] Within six hours, skeletal muscle weakness can be noted, although it commonly requires seven days for full clinical paralysis to be evident. This effect can last between 3 and 6 months, subverted by newly developed axons and neuromuscular junctions.[5]

BoNTA also prevents the release of substance P through the same mechanism.[7] This process is mediated by the molecule's light chain (L chain) through five steps: binding to the nerve terminal, internalization within the endocytic compartment, translocation of the L chain across vesicle membrane, release of the L chain into cytosol, and cleavage of SNARE proteins.[8]

There were traditionally seven serotype classifications of botulinum neurotoxin, each with distinct immunologic characteristics; next-generation sequencing has identified unique botulinum neurotoxins that promise novel properties and therapeutic indications.[8] BoNTA has proven to be the most efficacious for human use, with the best safety profile and widest therapeutic indications.[8,9] Each serotype of botulinum neurotoxin has a unique binding affinity and duration of action; this is an active area of research focused on new therapeutic toxins and indications.[10]

Botulinum toxin's effects on skeletal muscle are well established. The mechanisms whereby it affects pain pathways are less well known. Glutamate, CGRP, and substance P are known to be potent pain mediators and proinflammatory neuromodulators. Similar to motor nerves, sensory nerves are also capable of toxin uptake, and BoNTA has been shown to decrease or block the release of these pain mediators peripherally from nerve terminals and dorsal root ganglia, as well as central nerves within the spinal cord.[4,11–14] It has also been found to decrease inflammation around peripheral nerve terminals by inhibiting release of proinflammatory mediators, most importantly glutamate.[7] In addition, it downregulates the expression of cyclooxygenase 2, a key enzyme that converts arachidonic acid to prostaglandins—mediators of inflammation and pain.[15] The summation of these effects is believed to prevent sensitization of peripheral nerves, thereby inhibiting hyperactivity and reducing central sensitization.[4]

Similar to antiepileptic drugs, botulinum toxin has been shown to inhibit sodium channels.[16] This is important in the treatment of neuropathic pain because sodium channels propagate nerve impulses as afferent impulse electrical discharges.[17] By inhibiting sodium channels, nociceptive signals cannot be transmitted to the central nervous system.

There is emerging evidence to suggest that the A1 serotype undergoes retrograde transport within sensory neurons through active retroaxonal transport.[18,19] This was proven during investigations into the antinociceptive effects of BoNTA in treating rheumatoid and osteoarthritis pain via the downregulation of the transient receptor potential vanilloid 1 (TRPV1) channel.[20] TRPV1 channels are predominantly located in dorsal root ganglia and are involved in transmitting noxious stimuli to the central nervous system. Peripherally injected BoNTA was found within dorsal root ganglia and resulted in decreased expression of TRPV1. This provides further evidence to suggest that the toxin has systemic antinociceptive effects.[21–23]

PLASTIC SURGERY RELATED USES OF BOTULINUM TOXIN FOR PAIN

Migraine Headache: GRADE, High Quality

Table 2 lists the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) rating for the use of BoNTA in migraine headache.

Its U.S. Food and Drug Administration approval in 2010 for the treatment of chronic migraines (15 or more days/month) likely represents the most notable pain pathology that Botox (Allergan) has been shown to treat. The use of BoNTA for migraine headache was first reported in 1994, when it was discovered to incidentally relieve migraine headaches in patients being treated for hyperfunctional glabellar lines.[24] Early 2000 phase II data from randomized, controlled trials for the use of BoNTA for prophylaxis of migraine headache described significant findings in secondary

Table 2. Grading of Recommendations, Assessment, Development, and Evaluations[57]

GRADE Designation	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and/or may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluations.

endpoints, including a greater than 50 percent reduction in headache frequency, severity, and use of acute medication (level I evidence).[25,26] In 2011, Aurora et al.[27] published their 56-week PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) double-blind, parallel-group, placebo-controlled study in which 1384 patients were randomized into receiving five cycles, at 5-week intervals, consisting of 31 fixed-site, fixed-dose injections of 155 U of onabotulinumtoxin A, or 195 U across 39 sites (an additional 40 U was administered across the occipitalis, temporalis, and trapezius). The treatment group was found to have significant decreases in headache-day frequency, frequency of migraine days, moderate/severe headache days, and total headache hours on headache days (level I evidence).[27]

Current U.S. Food and Drug Administration approval for the use of Botox is based on the injection of 155 U across 31 sites. With the advent of migraine surgery, the plastic surgery community largely utilizes BoNTA as a tool for the diagnosis of cervicofacial migraine trigger sites in which to target peripheral nerves for surgical decompression.[28]

In 2015, Guyuron et al.[29] detailed their experience and algorithmic approach in the identification of trigger sites. Surgical decompression is based on the idea of peripherally mediated migraine headache secondary to the sensitization of trigeminal nerves at the peripheral level, followed by the release of proinflammatory neuropeptides, resulting in sterile meningitis and migraine headaches.[30] Although BoNTA has been shown to inhibit the release of proinflammatory neuropeptides, it is likely also its chemodenervating property in which compressive, irritating muscle contractions on peripheral nerves are inhibited, mitigating peripheral triggers of migraine headache.

This off-label approach has been studied as a long-term therapy for migraine headache, as retrospectively reported by Janis et al.[31] in 2017 (level III evidence). Rather than using the pattern approved by the Food and Drug Administration, Janis et al. offered lower-dose "targeted peripheral nerve–directed" Botox (Allegan) injections. Results showed significant improvement in Migraine Headache Index score (53.5 ± 83.0, $p < 0.006$), headache days/month (9.2 ± 12.7, $p < 0.0009$), and migraine severity (2.6 ± 2.5, $p < 0.00008$) as compared with baseline. Moreover, they reported continued Migraine Headache Index score improvement until "steady-state" injections were reached ($p < 0.002$), with follow-up of more than 600 days. Ultimately however, they reported better Migraine Headache Index score improvement with surgery as compared with long-term Botox ($p < 0.05$).

Common adverse events reported in the above studies were consistent with the known onabotulinumtoxin A safety profile. Most readily documented adverse events were muscular weakness, neck pain, blepharoptosis, and headache. Few patients withdrew from prospective studies secondary to intolerable adverse events.

Vasospastic Disorders of the Hand: GRADE, Low

The role for botulinum neurotoxin in the treatment of digital vessel vasospasm, or Raynaud phenomenon, has been discussed since 2004.[32] BoNTA is reported as beneficial in patients who have failed conservative/medical management and represents an alternative to digital artery sympathectomies. There exist several competing theories regarding the precise mechanism of action of BoNTA in vasospastic disorders of the hand,[33] including inhibition of sympathetic and sensory nerves, inhibition of inflammatory neuropeptides, regulation of signal transduction,[7,34,35] inhibition of smooth muscle contraction through alterations in calcium and nitric oxide sensitivity,[36] and blockage of norepinephrine release with decreased adrenergic receptor expression.[37]

Neumeister[38] has described his technique for injection in which patients receive 10 U of BoNTA adjacent to the neurovascular bundle just proximal to the A1 pulley. He retrospectively reported his experience in 2009 (level III evidence)[39] and 2010 (level III evidence).[38] In 2009, he described 19 patients with ischemic pain who received 50 to 100 U of Botox. Sixteen of 19 patients (84 percent) reported resolution of pain, with 13 reporting immediate relief. All patients with digital ulceration healed within 60 days. Twelve of 19 patients received only a single injection and remained pain-free at last follow-up (range, 13 to 59 months). More than 70 percent of patients (10 of 14) with laser Doppler scans of the hands demonstrated increased perfusion within 30 minutes of injection. The most notable complication was intrinsic muscle weakness ($n = 3$), lasting up to 2 months. His 2010 study detailed 28 of 33 patients (85 percent) reporting reduced pain at rest. Tissue perfusion via laser Doppler studies demonstrated a range from −48.15 percent to 317.39 percent change in blood flow to digits.

Several case reports have detailed the efficacy of BoNTA in the treatment of digital vasospasm.[32,37–40] Motegi et al.[37] (level V evidence)

reported 10 Japanese patients all with diagnosed systemic scleroderma and Raynaud's phenomenon. The most severely affected digit was injected with 10 U of BoNTA on both sides and proximal to the A1 pulley. Relative Raynaud scores decreased to 60 percent of baseline at 4 weeks ($p < 0.05$) and 40 percent at 16 weeks after injection ($p < 0.01$). In addition, pain rated on a visual analog scale decreased to 70 percent of baseline ($p < 0.05$) at 2 weeks and approximately 20 percent at 16 weeks after injection ($p < 0.01$). There was also an improvement ($p < 0.05$) in relative skin temperature recovery after cold stimuli as early as 4 weeks. All patients with intractable digital ulceration ($n = 5$) at time of injection healed their ulceration by 12 weeks. The only adverse event reported was injection site pain. They specifically note that reduction in muscle contraction force was not observed; however, no further detail is provided describing how this was measured.

Fregene and colleagues[40] (level III evidence) retrospectively reviewed their experience in 26 patients with Raynaud's. Injection sites varied from the distal palm along the superficial arch (83 percent) to the digital arteries (38 percent) and the proximal hand at the level of the radial and ulnar arteries (13 percent), with 42 percent of patients receiving multisite injections. An average of 77 U of Botox were injected per encounter (range, 10 to 100 U). Average visual analog scale score decreased from 8.1 ± 2.3 to 5.2 ± 2.5, representing a 35 percent pain reduction ($p < 0.01$). Transcutaneous oxygenation improved ($p < 0.05$), while subjective skin color change was not significantly altered ($p = 0.43$). Eleven of 23 patients (48 percent) with ulceration healed within 9.5 weeks of first injection, with nine digits proceeding to amputation. Intrinsic hand weakness was reported in six patients, without a statistically significant relationship to injection site, and resolved within 5 months.

Abdominal Wall Reconstruction: GRADE, Low Quality

Zendejas et al.[41] (level III evidence) reported their retrospective case-control series in patients undergoing incisional hernia repair with chemical component paralysis via BoNTA injections. The 300 U were dispersed among six injection sites (subcostal, anterior axillary, and lower quadrants bilaterally). Injections started within the transversus abdominis layer, with the external and internal oblique muscles being infiltrated on withdrawal.

Their series included 22 patients who underwent BoNTA chemical component paralysis and 66 controls. Thirteen patients received chemical component paralysis at the time of surgery, with the remaining receiving injections 1 to 19 days before surgery. All chemical component paralysis patients had underlay mesh placement, as compared with 77 percent of controls ($p < 0.02$) with three of them requiring prior mesh explantantion as compared with no controls ($p = 0.01$). Chemical component paralysis patients used fewer morphine equivalents on hospital days 2 and 5 and reported less pain on days 2 and 4 ($p < 0.007$). Although not statistically significant ($p = 0.08$) or available in all patients, hernia size in the chemical component paralysis group averaged 59.7 cm^2 ($n = 9$) as compared with 117.5 cm^2 in controls ($n = 39$). This group noted no BoNTA injection-related adverse events in their study cohort.

Phantom Limb Pain: GRADE, Very Low Quality

Phantom limb pain occurs after amputation; the etiology is multifactorial and can be broadly categorized as central, spinal, and peripheral in origin.[42] A case series by Jin et al.[43] detailed the injections of three lower extremity amputee patients with up to 500 U of BoNTA under electromyography guidance. They reported improvement on a three-point scale, as well as significant reduction in pain scores and pain medication use. Moreover, they reported improved prosthetic tolerability and gait stability while documenting no injection-related adverse events (level V evidence).

A prospective, randomized study of 14 amputee patients who received either 250 to 300 U of Botox or a combination of 1 percent lidocaine and 10 mg of methylprednisolone injected into each trigger point found immediate improvement in both groups lasting up to 6 months in residual limb pain and pain tolerance. Phantom limb pain was not improved. In addition, there was no statistically significant difference in residual limb or phantom limb pain between the two groups as measured by visual analog scores[44] (level II evidence). No adverse events were reported.

NON–PLASTIC SURGERY–RELATED USES OF BOTULINUM TOXIN FOR PAIN

Trigeminal Neuralgia: GRADE, Moderate

Trigeminal neuralgia presents as unilateral, electric-type pain, isolated to one or more divisions of the trigeminal nerve, and significantly impacts quality of life. Medical management is

often inconsistent and ineffective, with reported failure rates of 50 percent.[45]

A 2013 randomized, single blinded, placebo-controlled study[45] (level II evidence) detailed 20 patients with trigeminal neuralgia; 10 were injected with 40 to 60 U of BoNTA (5 U per site, eight to 12 sites) in a "follow the pain" method. Significant pain reduction was found at 12 weeks ($p < 0.0001$), with visual analog scores decreased by 6.5 in the treatment group as compared with 0.3 for the placebo group. There was a decrease in the amount of acute weekly medications being used ($p < 0.001$) and an increase in quality-of-life metrics ($p < 0.0001$). Complications included facial asymmetry in four treatment patients.

A 2016 prospective study[46] (level II evidence) detailed 87 patients with single-branch trigeminal neuralgia who received 75 to 100 U of BoNTA along 15 to 20 sites. Visual analog scale scores decreased ($p < 0.001$) weekly, with baseline scores of 6.59 ± 2.18 and week 8 scores reported as 1.95 ± 1.96 ($p < 0.001$). Anxiety and depression scores decreased every week ($p < 0.001$). Sleep interference scores were also decreased ($p < 0.01$), while quality-of-life measures increased ($p < 0.01$).

In addition, a 2014 randomized, double blinded, placebo-controlled trial compared low-dose (25 U) and high-dose (75 U) BoNTA versus placebo in 80 patients. Visual analog scale scores were reduced at week 1 and were sustained through week 8 for both groups ($p < 0.017$, $p < 0.017$). Using the Patient Global Impression of Change to determine intervention response, 67 percent (25 U) and 76 percent (75 U) reported symptoms as being at least much improved as compared with the placebo group (level II evidence).[47] Reported adverse events included three patients with facial asymmetry (two in the 25-U cohort and one in the 75-U cohort) and transient injection site edema in two patients.

Lastly, a 2018 meta-analysis[48] (level I evidence) reviewed 495 patients (266 BoNTA and 229 saline), comparing the use of BoNTA for the treatment of neuralgia. The authors reported a significant reduction in pain for the BoNTA group as compared with the saline group at 4 weeks ($p = 0.04$), 12 weeks ($p < 0.00001$), and 24 weeks ($p = 0.009$). There was no difference in sleep or quality of life. Of note, in the trigeminal neuralgia subset ($n = 104$), 14 patients (12.9 percent) reported facial asymmetry following injection.

Postherpetic Neuralgia: GRADE, Moderate

Postherpetic neuralgia is an extremely painful, difficult-to-treat sequela following the reactivation of zoster virus. Targeting the antinociceptive effects of BoNTA, Xiao et al.[49] reported their randomized, double-blinded, placebo-controlled study in which BoNTA was compared against 0.5 percent lidocaine and saline placebo in 60 patients. Visual analog scale pain reporting decreased for the BoNTA group as compared with both the lidocaine and placebo groups at day 7 and 3 months ($p < 0.01$). Mean pain scores decreased by 4.5 in the BoNTA group, as compared with 2.6 and 2.9 in the lidocaine and placebo groups, respectively ($p < 0.05$). The BoNTA cohort showed improved sleep, a quality-of-life measure, at day 1 and 3 months ($p < 0.01$), as well as decreased opioid use at day 7 and 3 months ($p < 0.01$) (level II evidence).[49] No adverse events other than injection site pain were reported.

In addition, Apalla et al.[50] reported their 30-patient, randomized, double-blind, placebo-controlled trial in patients with postherpetic neuralgia. All treatment patients received 100 U of BoNTA to the surrounding area of tactile allodynia. Among the treatment patients, 87 percent ($n = 13$) experienced a minimum 50 percent reduction from the preinjection visual analog scale score, while none in the placebo group met this metric ($p < 0.001$). Pain improvement was achieved at day 7 on average and was sustained for up to 16 weeks. The treatment group also experienced improved sleep, which continued until week 16 ($p < 0.001$) (level II evidence).[50] Injection site pain was the only reported tolerability issue in this study. However, no patients withdrew from the study and none were able to recognize treatment based on discomfort.

Diabetic Neuropathy: GRADE, Moderate

The Centers for Disease Control and Prevention estimates that 9.4 percent of the U.S. population is diagnosed with diabetes, with 30 percent to 50 percent developing peripheral neuropathy during their lifetime.[51] While anticonvulsants and antidepressants remain the mainstay of treatment, BoNTA has been investigated for the treatment of diabetic neuropathy. In a double-blind crossover control trial,[52] 18 patients with diabetic neuropathy underwent 12 injections of 50 U total of BoNTA into the dorsum of the foot; the control group received saline (level II evidence). There were significant reductions in the BoNTA cohort's visual analog scale scores at 1, 4, 8, and 12 weeks ($p < 0.05$). A similar double-blind randomized control trial of 40 patients with diabetic neuropathy reported 20 patients who received 100 U of BoNTA to the dorsum of the foot.[53] The treatment group showed a significant reduction

in visual analog scale pain scores as compared with the placebo group ($p < 0.01$), as well as reduced scores for electric shocks, burning pain, and pins and needles sensation ($p < 0.05$) (level II evidence).

Urology: GRADE, Moderate Quality

A meta-analysis of intravesical botulinum toxin for interstitial cystitis and bladder pain found that botulinum toxin improved pelvic pain and interstitial cystitis scores and decreased daytime urination (level I evidence).[54] The only significant adverse event noted was increased postvoid residual, as noted in four of the studies. Moreover, a double-blind, randomized, placebo controlled trial of 60 women with chronic pelvic pain found a significant reduction in dyspareunia and nonmenstrual pelvic pain scores after injection of 80 U of BoNTA into the pelvic floor muscles (level I evidence).[55] The most common adverse event was vaginal bleeding at the injection site. Otherwise, there were no significant adverse events within the treatment group as compared with the control group. A further prospective open-label pilot study of 21 women with high-tone pelvic floor dysfunction who underwent injection of up to 300 U of BoNTA via electromyography guidance found improvement in Global Response Assessment, dyspareunia visual analog scale, Female Sexual Distress Scale, and quality-of-life scores (level II evidence).[56] Notable adverse events centered on worsening of preexisting conditions (i.e., constipation, stress urinary incontinence, and fecal incontinence). New-onset urinary incontinence developed in one patient.

CONCLUSIONS

The evolution of botulinum neurotoxin from a cosmetic agent to a treatment modality for multiple painful pathologies represents an exciting and minimally invasive treatment option for many patients. As we identify additional pathologies amenable to this intervention, it is arguably more important to further elucidate botulinum neurotoxin's mechanism of action in the treatment of pain. If we can more clearly understand its ideal site of interference on peripheral triggers of pain, we may be able to more aptly apply it to painful pathologies in the future.

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REFERENCES

1. *IASP Terminology*. 2017. Available from: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698 - Pain. Accessed May 2018.
2. Cohen SP, Raja SN. Pain. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. New York: Elsevier Saunders; 2016.
3. *FDA approved drug products*. Biologic license application: 10300, Company: Allergan. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103000. Accessed November 11, 2018.
4. Nahabet E, Janis JE, Guyuron B. Neurotoxins: expanding uses of neuromodulators in medicine—Headache. *Plast Reconstr Surg*. 2015;136(5 Suppl):104S–110S.
5. Rohrich RJ, Janis JE, Fagien S, Stuzin JM. The cosmetic use of botulinum toxin. *Plast Reconstr Surg*. 2003;112(5 Suppl):177S–188S.
6. Rossetto O, Pirazzini M, Montecucco C. Botulinum neurotoxins: Genetic, structural and mechanistic insights. *Nat Rev Microbiol*. 2014;12:535–549.
7. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain* 2004;107:125–133.
8. Pirazzini M, Rossetto O, Eleopra R, Montecucco C. Botulinum neurotoxins: Biology, pharmacology, and toxicology. *Pharmacol Rev*. 2017;69:200–235.
9. Naumann M, Dressler D, Hallett M, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of secretory disorders. *Toxicon* 2013;67:141–152.
10. Sikorra S, Litschko C, Müller C, et al. Identification and characterization of botulinum neurotoxin A substrate binding pockets and their re-engineering for human SNAP-23. *J Mol Biol*. 2016;428(2 Pt A):372–384.
11. Oh HM, Chung ME. Botulinum toxin for neuropathic pain: A review of the literature. *Toxins (Basel)* 2015;7:3127–3154.
12. Meng J, Wang J, Lawrence G, Dolly JO. Synaptobrevin I mediates exocytosis of CGRP from sensory neurons and inhibition by botulinum toxins reflects their anti-nociceptive potential. *J Cell Sci*. 2007;120(Pt 16):2864–2874.
13. Reynolds WS, Gottlieb LJ, Lucioni A, Rapp DE, Song DH, Bales GT. Vesicovaginal fistula repair with rectus abdominus myofascial interposition flap. *Urology* 2008;71:1119–1123.
14. Kim HS, Lee HW, Kim WS, Ko YH. Systemic Epstein-Barr virus-negative mature natural killer-cell lymphoma with cutaneous and visceral involvement. *APMIS* 2015;123:990–992.
15. Chuang YC, Yoshimura N, Huang CC, Wu M, Chiang PH, Chancellor MB. Intraprostatic botulinum toxin A injection inhibits cyclooxygenase-2 expression and suppresses prostatic pain on capsaicin induced prostatitis model in rat. *J Urol*. 2008;180:742–748.
16. Shin MC, Wakita M, Xie DJ, et al. Inhibition of membrane Na+ channels by A type botulinum toxin at femtomolar concentrations in central and peripheral neurons. *J Pharmacol Sci*. 2012;118:33–42.
17. Devor M. Sodium channels and mechanisms of neuropathic pain. *J Pain* 2006;7(1 Suppl 1):S3–S12.
18. Restani L, Antonucci F, Gianfranceschi L, Rossi C, Rossetto O, Caleo M. Evidence for anterograde transport and transcytosis of botulinum neurotoxin A (BoNT/A). *J Neurosci*. 2011;31:15650–15659.
19. Matak I, Bach-Rojecky L, Filipović B, Lacković Z. Behavioral and immunohistochemical evidence for central antinociceptive activity of botulinum toxin A. *Neuroscience* 2011;186:201–207.
20. Fan C, Chu X, Wang L, Shi H, Li T. Botulinum toxin type A reduces TRPV1 expression in the dorsal root ganglion in rats with adjuvant-arthritis pain. *Toxicon* 2017;133:116–122.

21. Matak I, Lacković Z. Botulinum toxin A, brain and pain. *Prog Neurobiol.* 2014;119-120:39–59.
22. Mazzocchio R, Caleo M. More than at the neuromuscular synapse: Actions of botulinum neurotoxin A in the central nervous system. *Neuroscientist* 2015;21:44–61.
23. Pellett S, Yaksh TL, Ramachandran R. Current status and future directions of botulinum neurotoxins for targeting pain processing. *Toxins (Basel)* 2015;7:4519–4563.
24. Keen M, Blitzer A, Aviv J, et al. Botulinum toxin A for hyperkinetic facial lines: Results of a double-blind, placebo-controlled study. *Plast Reconstr Surg.* 1994;94:94–99.
25. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C; BOTOX CDH Study Group. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. *Headache* 2005;45:293–307.
26. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD; BOTOX CDH Study Group. Botulinum toxin type A for the prophylaxis of chronic daily headache: Subgroup analysis of patients not receiving other prophylactic medications: A randomized double-blind, placebo-controlled study. *Headache* 2005;45:315–324.
27. Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled analyses of the 56-week PREEMPT clinical program. *Headache* 2011;51:1358–1373.
28. Kung TA, Guyuron B, Cederna PS. Migraine surgery: A plastic surgery solution for refractory migraine headache. *Plast Reconstr Surg.* 2011;127:181–189.
29. Guyuron B, Nahabet E, Khansa I, Reed D, Janis JE. The current means for detection of migraine headache trigger sites. *Plast Reconstr Surg.* 2015;136:860–867.
30. Buzzi MG, Tassorelli C, Nappi G. Peripheral and central activation of trigeminal pain pathways in migraine: Data from experimental animal models. *Cephalalgia* 2003;23(Suppl 1):1–4.
31. Janis JE, Barker JC, Palettas M. Targeted peripheral nerve-directed onabotulinumtoxin A injection for effective long-term therapy for migraine headache. *Plast Reconstr Surg Glob Open* 2017;5:e1270.
32. Sycha T, Graninger M, Auff E, Schnider P. Botulinum toxin in the treatment of Raynaud's phenomenon: A pilot study. *Eur J Clin Invest.* 2004;34:312–313.
33. Neumeister MW. The role of botulinum toxin in vasospastic disorders of the hand. *Hand Clin.* 2015;31:23–37.
34. Setler PE. Therapeutic use of botulinum toxins: Background and history. *Clin J Pain.* 2002;18(6 Suppl):S119–S124.
35. Cheng CM, Chen JS, Patel RP. Unlabeled uses of botulinum toxins: A review, Part 1. *Am J Health Syst Pharm.* 2006;63:145–152.
36. Fonseca C, Abraham D, Ponticos M. Neuronal regulators and vascular dysfunction in Raynaud's phenomenon and systemic sclerosis. *Curr Vasc Pharmacol.* 2009;7:34–39.
37. Motegi S, Yamada K, Toki S, et al. Beneficial effect of botulinum toxin A on Raynaud's phenomenon in Japanese patients with systemic sclerosis: A prospective, case series study. *J Dermatol.* 2016;43:56–62.
38. Neumeister MW. Botulinum toxin type A in the treatment of Raynaud's phenomenon. *J Hand Surg Am.* 2010;35:2085–2092.
39. Neumeister MW, Chambers CB, Herron MS, et al. Botox therapy for ischemic digits. *Plast Reconstr Surg.* 2009;124:191–201.
40. Fregene A, Ditmars D, Siddiqui A. Botulinum toxin type A: A treatment option for digital ischemia in patients with Raynaud's phenomenon. *J Hand Surg Am.* 2009;34:446–452.
41. Zendejas B, Khasawneh MA, Srvantstyan B, Jenkins DH, Schiller HJ, Zielinski MD. Outcomes of chemical component paralysis using botulinum toxin for incisional hernia repairs. *World J Surg.* 2013;37:2830–2837.
42. Hsu E, Cohen SP. Postamputation pain: Epidemiology, mechanisms, and treatment. *J Pain Res.* 2013;6:121–136.
43. Jin L, Kollewe K, Krampfl K, Dengler R, Mohammadi B. Treatment of phantom limb pain with botulinum toxin type A. *Pain Med.* 2009;10:300–303.
44. Wu H, Sultana R, Taylor KB, Szabo A. A prospective randomized double-blinded pilot study to examine the effect of botulinum toxin type A injection versus lidocaine/Depomedrol injection on residual and phantom limb pain: Initial report. *Clin J Pain* 2012;28:108–112.
45. Shehata HS, El-Tamawy MS, Shalaby NM, Ramzy G. Botulinum toxin-type A: Could it be an effective treatment option in intractable trigeminal neuralgia? *J Headache Pain* 2013;14:92.
46. Xia JH, He CH, Zhang HF, et al. Botulinum toxin A in the treatment of trigeminal neuralgia. *Int J Neurosci.* 2016;126:348–353.
47. Zhang H, Lian Y, Ma Y, et al. Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: Observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. *J Headache Pain* 2014;15:65.
48. Meng F, Peng K, Yang JP, Ji FH, Xia F, Meng XW. Botulinum toxin-A for the treatment of neuralgia: A systematic review and meta-analysis. *J Pain Res.* 2018;11:2343–2351.
49. Xiao L, Mackey S, Hui H, Xong D, Zhang Q, Zhang D. Subcutaneous injection of botulinum toxin A is beneficial in postherpetic neuralgia. *Pain Med.* 2010;11:1827–1833.
50. Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: A parallel, randomized, double-blind, single-dose, placebo-controlled trial. *Clin J Pain* 2013;29:857–864.
51. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. *Neurology* 2017;88:1958–1967.
52. Yuan RY, Sheu JJ, Yu JM, et al. Botulinum toxin for diabetic neuropathic pain: A randomized double-blind crossover trial. *Neurology* 2009;72:1473–1478.
53. Ghasemi M, Ansari M, Basiri K, Shaigannejad V. The effects of intradermal botulinum toxin type A injections on pain symptoms of patients with diabetic neuropathy. *J Res Med Sci.* 2014;19:106–111.
54. Wang J, Wang Q, Wu Q, Chen Y, Wu P. Intravesical botulinum toxin A injections for bladder pain syndrome/interstitial cystitis: A systematic review and meta-analysis of controlled studies. *Med Sci Monit.* 2016;22:3257–3267.
55. Abbott JA, Jarvis SK, Lyons SD, Thomson A, Vancaille TG. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: A randomized controlled trial. *Obstet Gynecol.* 2006;108:915–923.
56. Morrissey D, El-Khawand D, Ginzburg N, Wehbe S, O'Hare P 3rd, Whitmore K. Botulinum toxin A injections into pelvic floor muscles under electromyographic guidance for women with refractory high-tone pelvic floor dysfunction: A 6-month prospective pilot study. *Female Pelvic Med Reconstr Surg.* 2015;21:277–282.
57. Atkins D, Best D, Briss PA, et al.; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.