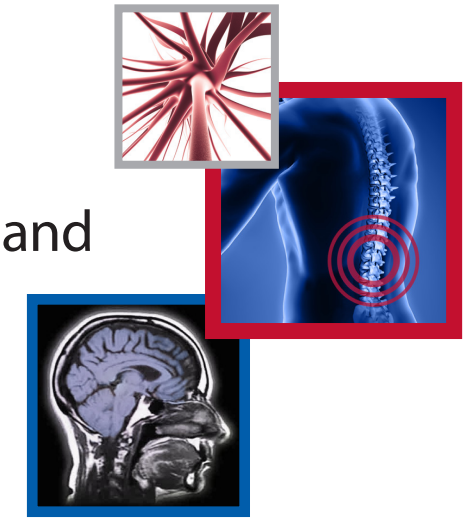
REVIEW



Botulinum toxin for neuropathic pain and spasticity: an overview

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Practice Points

- Based on evidence of its involvement in nociceptive transmission, botulinum toxin (BoNT) has been studied for the management of neuropathic pain.
- BoNT is a safe and effective treatment for spasticity in adults (level A evidence), and has been shown to decrease muscle tone, pain, disability and caregiver burden.
- There is level A evidence for established efficacy of BoNT injection in postherpetic neuralgia.
- There is level B evidence for probable efficacy of BoNT injection in trigeminal neuralgia and post-traumatic neuralgia.
- There is level B evidence for probable lack of efficacy of BoNT injection in carpal tunnel syndrome.
- There is level C evidence for possible efficacy of BoNT injection in diabetic polyneuropathy.
- There is level U (insufficient) evidence for BoNT injection in complex regional pain syndrome, phantom limb and stump pain, and occipital neuralgia.

SUMMARY In recent years, a large body of data has surfaced reporting the therapeutic benefit of botulinum toxin injection in multiple conditions. The aim of this review is: to summarize the highest quality literature pertaining to clinical application of botulinum toxin in neuropathic pain conditions including postherpetic neuralgia, trigeminal neuralgia, diabetic polyneuropathy, post-traumatic neuralgia, carpal tunnel syndrome, complex regional pain syndrome, phantom limb and stump pain, and occipital neuralgia; to provide an overview of the clinical trials using botulinum toxin in adult spasticity; and to assign levels of evidence according to the American Academy of Neurology guidelines. In summary, there is level A evidence for established efficacy in postherpetic neuralgia and adult spasticity; level B evidence for probable efficacy in trigeminal neuralgia and post-traumatic neuralgia; level B evidence for probable lack of efficacy in carpal tunnel syndrome; level C evidence for possible efficacy in diabetic polyneuropathy; and level U (insufficient) evidence in complex regional pain syndrome, phantom limb and stump pain, and occipital neuralgia.

Botulinum neurotoxin (BoNT), derived from *Clostridium botulinum*, has been used therapeutically in a wide range of medical conditions. Serotype A (BoNT-A) is used most commonly and includes onabotulinumtoxinA (Botox®, Allergan, CA, USA), abobotulinumtoxinA

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(Dysport®, Ipsen Pharma), incobotulinumtoxinA (Xeomin®, Merz, NC, USA), and a Chinese preparation (Prosigne, Kowloon, Hong Kong); serotype B (BoNT-B) includes rimabotulinumtoxinB (Myobloc®, Solstice Neurosciences, CA, USA) [1]. BoNT's therapeutic value has been ascribed to its action at the SNARE complex located at the presynaptic nerve terminal. Specifically, BoNT-A interferes with vesicular docking and subsequent neurotransmitter release by cleaving SNAP-25 of the SNARE complex, while BoNT-B produces a similar effect by cleaving VAMP [2]. BoNT therefore interferes with ACh release at the neuromuscular junction leading to decreased muscle contraction; herein lies the benefit of therapeutic injection of BoNT in disorders of excessive muscle contraction.

Interestingly, there is evidence that BoNT also inhibits vesicular release of substance P [3], CGRP [4], and glutamate [5] by acting at the same SNARE protein complex [6]. Additionally, there is evidence of BoNT leading to a reduction in vanilloid receptor activity, TRPV1 (transient receptor potential cation channel subfamily V member 1), which is involved in integrating noxious stimuli [7,8]. These neuropeptides are involved in nociceptive signaling and their overactivity has been implicated in certain conditions of chronic pain. Thus, there has been an increase in attention in the pain community over the therapeutic potential of BoNT in neuropathic pain conditions [6].

Based on the antinociceptive mechanism hypothesis of BoNT, a large array of published data ranging from case reports to a few randomized controlled clinical trials has surfaced following injection of BoNT in various neuropathic pain syndromes. The neuropathic pain syndromes with the largest compilation of data, and therefore, on which this review will focus, include postherpetic neuralgia, trigeminal neuralgia, post-traumatic neuralgia, carpal tunnel syndrome, diabetic polyneuropathy, complex regional pain syndrome (CRPS), phantom limb and stump pain, and occipital neuralgia. Pain conditions including headache, migraine, back pain, myofascial pain, piriformis syndrome, brachial plexopathy, and pain resulting from neuromas and multiple sclerosis are beyond the scope of this review.

Spasticity is characterized by increased muscle tone in the setting of upper motor neuron dysfunction, which may occur secondary to a variety of processes, such as stroke, multiple sclerosis, traumatic brain injury and neoplasm [9,10]. Clinically, spasticity can cause limitations of active and passive muscle function leading to pain, disability, limb deformities and contractures, and decreased quality of life. Treatment options for adult spasticity include pharmacological and nonpharmacological interventions, such as botulinum toxin, tizanidine, benzodiazepines, baclofen, physical/occupational therapy, braces and splinting, tendon release surgery and rhizotomy [9].

BoNT has an important role in the management of adult spasticity due to its inhibition of ACh release at the neuromuscular junction. Most clinical trials investigating the use of BoNT in adult spasticity focus on outcome measures assessing muscle tone, pain and disability. While onabotulinumtoxinA has been approved in 2010 by the US FDA to treat spasticity of the flexor muscles of the elbow, wrist, and fingers in adults, the different formulations of BoNT have been widely used to treat other muscle groups in clinical practice. Recent evidence-based reviews by the American Academy of Neurology and two international consensus committees came to the conclusion that BoNT is a safe and efficacious treatment for adult spasticity [9–11]. Treatment-associated adverse effects include injection site reactions and muscle weakness, and are usually mild and self-limited if appropriate doses of BoNT are used to treat limb spasticity [12,13].

The goal of this review is to provide a compilation of the published data in which BoNT injection has been used in conditions of postherpetic neuralgia, trigeminal neuralgia, post-traumatic neuralgia, carpal tunnel syndrome, diabetic polyneuropathy, CRPS, phantom limb and stump pain, occipital neuralgia and adult spasticity.

There are a number of potential limitations to this review. While performing a literature search for high quality, placebo-controlled, double-blind investigations, it is clear that there is a paucity of such studies involving BoNT injection in conditions of neuropathic pain. Those studies that were identified utilize various forms of BoNT in differing dosages and patterns of administration. Additionally, by choosing not to review reports that exist only in abstract form, we may have inadvertently excluded some of the negative studies using BoNT.

Methods

A literature search was performed using MEDLINE (OvidSP platform), PubMed and the

Table 1. Botulinum toxin for postherpetic neuralgia.

Study (year)	Class	Design	Cohort size	Treatment (serotype/ brand/dose)	Follow-up	Outcome measures	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Liu *et al.* (2006)	IV	N/A	1	A/Botox® (Allergan, CA, USA)/100 U sc. divided over 20 sites in a fan pattern	N/A	Pain severity by VAS	N/A	Not mentioned	Pain severity decreased to 1 from baseline of 10; effect gradually seen by day 2, lasted total of 52 days	Case report; no statistical analysis provided; case involved T2–4 dermatomes	[16]
Sotiriou *et al.* (2009)	IV	N/A	3	A/Botox/100 U sc. divided over 20 injections in chessboard pattern	Week 2, 4, 6, 8, 10, 12	Pain severity by VAS	None	Transient injection-related pain and erythema	VAS decreased within 72 h, max response within 7 days, persisted for 64 days	Case series; no statistical analysis provided; all three cases involved thoracic dermatomes	[17]
Klein *et al.* (2004)	IV	Case report	1	A/Botox/20 U intradermally	N/A	Pain intensity	N/A	Not mentioned	Complete relief of neuralgia pain for at least 4 months	Case involved L2–3 dermatomes	[18]
Xiao *et al.* (2010)	I	Randomized, double-blind, placebo-controlled study	60, 20 per arm (BoNT-A, lidocaine, placebo)	A/Lanzhou preparation, China: 5 U/ml sc. injections	Day 1, 7, month 3	Pain severity by VAS, sleep quality by hours, opiate use	4	Transient injection-related pain, no difference between groups	VAS decreased in all three groups, although more significantly in BoNT-A group; lidocaine reached peak effectiveness at day 1, better than BoNT-A or placebo at this time point; sleep increased in all groups, more significantly in BoNT-A group; significantly reduced opiate use in BoNT-A group at day 7 and month 3 compared with lidocaine or placebo	Chinese preparation of BoNT-A used; unspecified total dose of BoNT-A, simply mentioned that less than 200 U	[19]
Apalla *et al.* (2013)	I	Randomized, double-blind, 2-arm, single-dose, placebo-controlled, parallel clinical trial; transitions over to open-label phase between weeks 4 and 24	30 (four excluded because of low baseline VAS), 15 per arm (BoNT-A, placebo)	A/Botox/100 U sc. divided over 40 injections in a chessboard pattern	Week 2, 4. Then open-label phase weeks 6, 8, 10, 12, 16, 20, 24	Pain severity by VAS within first 4 weeks†; clinical significance defined as >50% reduction from baseline level; reduction in sleep score and maintenance of VAS score beyond 4 weeks postinjection‡	None	Transient injection-related pain, no difference between groups	87% BoNT patients achieved ≥50% reduction in VAS, significant at weeks 2 and 4; NNT = 1.2; effect not observed in placebo†; BoNT patients with significant improvement in sleep between weeks 2–12‡; nonsignificant improvement in placebo at weeks 2 and 4; maintenance of VAS from weeks 4–16 in BoNT patients	Blinding removed after week 4 onward in the open-phase portion; majority of cases involved thoracic dermatomes (12/15 in treatment group and 13/15 in placebo group)	[20]

†Primary result; ‡Secondary result.
BoNT: Botulinum toxin; N/A: Not applicable; NNT: Number-needed-to-treat; sc.: Subcutaneous; VAS: Visual analog scale.

Table 2. Botulinum toxin for trigeminal neuralgia.

Study (year)	Class	Design	Cohort size	Treatment (serotype/brand/dose)	Follow-up	Outcome measures	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Wu *et al.* (2012)	I	Randomized, double-blind, placebo-controlled, parallel design	42 (22 in BoNT-A, 20 in placebo groups)	A/Lanzhou preparation, China/75 U intradermal or submucosal	12 weeks	Pain severity by VAS and self-reported attack frequency†; PGIC‡	One in each group	Five patients injected with BoNT-A with facial asymmetry lasting up to 7 weeks, three patients with transient injection site edema	Significant decrease in VAS from week 2 to completion of study, significant decrease in attack frequency from week 1 to completion of study, significant improvement of PGIC	Chinese preparation of BoNT used, which is not interchangeable with other preparations; study duration only 12 weeks	[21]
Bohluli *et al.* (2011)	IV	Open-label trial	15	A/unspecified preparation/ 50–100 U per trigger point	1 week, 1 month, 6 months	Pain severity, attack frequency, patient overall response to treatment via Patient Global Assessment Scale	None	Three patients with partial facial paresis lasting up to 2 weeks in two patients and 3 months in another	Significant improvement in all measures, eradication of pain in seven patients	Unspecified BoNT-A preparation used, unspecified depth of injection, study design includes no placebo, unblinded	[22]
Ngeow and Nair (2010)	IV	N/A	1	A/Botox® (Allergan, CA, USA)/100 U sc. divided over two trigger zones	N/A	Subjective pain report	N/A	Mild facial weakness	Resolution of nasal pain at day 2, partial mental pain relief	Case report	[29]
Turk *et al.* (2005)	IV	Open-label trial	8	A/Botox/100 U divided into two sites above and below zygomatic arch, depth 1.5–2 cm	1 week, 2 months, 6 months	Pain severity by VAS, attack frequency	None	None major; one patient with transient dysesthesia, another with transient chewing difficulty	Significant decrease in VAS pain and attack frequency at 1 week, 2 months, 6 months (compared with baseline)	Low VAS pain level baseline of 4	[23]
Piovesan *et al.* (2005)	IV	Open-label pilot study	13	A/unspecified preparation: varying doses of transcutaneous injections based on area performed in a grid pattern (mean therapeutic coefficient 3.22 U/cm^2)	Day 10, 20, 30, 60	Pain severity by VAS, pain surface area, preventive medication consumption	None	None major; three with facial asymmetry; one with slight ptosis	Significant reduction of pain by VAS and pain surface area beginning at day 10, peak effect at 20 days, effect persisted beyond 60 days. Four patients stopped preventive medication, all others reduced by at least 50% at day 60	Unspecified BoNT-A preparation used, study stopped prior to cessation of response, individual data not published	[24]

†Primary outcome measures; ‡Secondary outcome measures.
BoNT: Botulinum toxin; CPT: Current perception threshold; N/A: Not applicable; ON: Occipital neuralgia; PGIC: Patient Global Impression of Change Scale; sc.: Subcutaneous; VAS: Visual analog scale.

Table 2. Botulinum toxin for trigeminal neuralgia (cont.).

Study (year)	Class	Design	Cohort size	Treatment (serotype/brand/dose)	Follow-up	Outcome measures	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Zuniga *et al.* (2008)	IV	Open-label case series	12	A/Botox/20–50 U sc. divided into trigger zones	Week 1, 2, 3, 4, 5, 6, 7, 8	Pain severity by VAS	None	One patient with transient facial asymmetry	Reportedly significant reduction in VAS in ten patients	No statistical analysis is provided of VAS reduction in comparison to baseline	[25]
Borodic and Acquadro (2002)	IV	Open-label pilot study	11	A/Botox/30–50 U injected 1–3 mm deep, 10 mm apart	Week 2, 6	Pain reduction (responder if >50% pain intensity or frequency reduction), reduction in analgesic use	None	Mild facial asymmetry and weakness	Eight out of 11 patients experienced >50% reduction in pain frequency or intensity	No control	[26]
Micheli *et al.* (2002)	IV	N/A	1	A/Botox/15 U divded over six sites including orbicularis oris and buccinator	N/A	Subjective pain report	N/A	Not listed	Reduction in pain and twitching	Case report; condition of painful tic convulsif; depth of injections are not specified	[31]
Volcy *et al.* (2005)	IV	N/A	1	A/unspecified preparation/15 U right ON, 7.5 U at left masseter and zygomatic muscles; repeat injections of 12 U right ON, 6 U at left masseter and zygomatic muscles	N/A	Subjective pain report	N/A	None	Temporary relief of pain, cessation of analgesic overuse	Case report; unspecified BoNT preparation	[27]
Yoon *et al.* (2010)	IV	N/A	1	A/Botox/10 U sc. middle of chin	1 month, 2 months	Subjective pain report, CPT evaluation	N/A	Not provided	Decreased area of pain at 1 month, decreased pain intensity at 2 months, decreased CPT levels at all frequencies at months 1 and 2	Case report; trigeminal neuralgia resulting from traumatic dental surgery injury to inferior alveolar nerve branch of trigeminal nerve. Unclear relationship between CPT measurement and clinical benefit	[28]

†Primary outcome measures; ‡Secondary outcome measures.
BoNT: Botulinum toxin; CPT: Current perception threshold; N/A: Not applicable; ON: Occipital neuralgia; PGIC: Patient Global Impression of Change Scale; sc.: Subcutaneous; VAS: Visual analog scale.

Table 2. Botulinum toxin for trigeminal neuralgia (cont.).

Study (year)	Class	Design	Cohort size	Treatment (serotype/brand: dose)	Follow-up	Outcome measures	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Allam *et al.* (2005)	IV	N/A	1	A/Botox/16 U sc. divided into eight trigger points	Day 7, 30, 60, 90	Pain severity by VAS	N/A	Mild facial asymmetry	Reduction in VAS persistent beyond day 90, no longer needed oral adjunctive therapy	Case report; interestingly, patient reported pain reduction in V3 even though only V1–2 were injected. Study terminated prior to cessation of response	[30]
Felicio *et al.* (2006)	IV	N/A	1	A/unspecified preparation: 100 U on left, 52 U on right	N/A	Subjective pain report	N/A	Not listed	Reduction in twiching and pain after second injection (5 months after first injection)	Case report; condition of painful tic convulsif	[32]

†Primary outcome measures; ‡Secondary outcome measures.
BoNT: Botulinum toxin; CPT: Current perception threshold; N/A: Not applicable; ON: Occipital neuralgia; PGIC: Patient Global Impression of Change Scale; sc.: Subcutaneous; VAS: Visual analog scale.

Cochrane Database to identify peer-reviewed, pertinent, English articles on human subjects published during February 2013 with search terms including, but not limited to: 'Botulinum Toxin,' 'Botox,' 'onabotulinumtoxinA,' 'Dysport,' 'abobotulinumtoxinA,' 'Xeomin,' 'incobotulinumtoxinA,' 'Myobloc,' 'rimobotulinumtoxinB,' 'neuropathic pain,' 'neuropathy,' 'neuralgia,' 'postherpetic neuralgia,' 'trigeminal neuralgia,' and 'spasticity'. All citations from articles were checked to identify additional relevant sources. Papers were read and classified according to American Academy of Neurology criteria into Class I, Class II, Class III, and Class IV categories. Based on this classification, level evidence was assigned (Level A, Level B, Level C or Level U) [14].

Neuropathic pain conditions

Neuropathic pain stems from injury to the peripheral or CNS [7,15]. The quality of this type of pain is often described as stabbing, burning, and electrical. As neuropathic pain is often refractory to medical management, many physicians have attempted BoNT injection in an effort to manage the following neuropathic pain conditions:

■ Postherpetic neuralgia

After several encouraging case reports and small case series [16–18], Xiao *et al.* conducted a class I randomized, double-blind, placebo-controlled study which looked at the effects of subcutaneous injection with either a Chinese preparation of BoNT-A (Lanzhou Institute, China), lidocaine, or placebo in patients with refractory postherpetic neuralgia, the majority with thoracic involvement. The investigators determined if there was an improvement in three measures including pain severity by visual analog scale (VAS), hours of sleep, and reduction of opioid use following injections. The group found that all groups experienced significant improvement ($p < 0.01$) at 7 days and 3 months in all measures, and that the improvement in the BoNT-A group was significantly better ($p < 0.01$) than the improvement in the other groups [19].

Apalla *et al.* reported that 30 patients with mostly thoracic postherpetic neuralgia were randomized to receive subcutaneous injections of either 100 U of onabotulinumtoxinA or placebo in a double-blind, two-arm, single-dose, placebo-controlled clinical trial. The patient's pain severity was measured by VAS. All patients

Table 3. Botulinum toxin for post-traumatic neuralgia.

Study (year)	Class	Design	Cohort size	Treatment (serotype/brand/dose)	Follow-up	Outcome measures	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Ranoux *et al.* (2008)	I	Randomized, double-blind, placebo-controlled, parallel group trial	29	A/Botox® (Allergan, CA, USA)/5 U intradermally per site × 20 sites	Week 4, 12, 24	Self-reported weekly mean pain score†; quantified testing of thermal and mechanical perception and pain, allodynia, neuropathic symptoms, clinical global impression, quality of life‡	7	Transient injection-site pain	Significant improvement in weekly average pain intensity, from week 2 and intermittently until 14 weeks†; decreased allodynia to brush and cold; improved VAS at weeks 4, 12, 24; global pain relief, improvement in three of five neuropathic symptoms including burning, electric shocks, stabbing; decreased pain paroxysms, improved general activity and mood; improved average pain intensity; improved anxiety scores	Diverse population of neuropathic pain conditions (25 of whom have post-traumatic or postoperative neuropathic pain)	[33]
Wittekindt *et al.* (2006)	IV	Open-label prospective randomized Phase II clinical trial comparing two doses	23	A/Dysport® (Ipsen Pharma)/10 MU/0.1 ml saline (low dose) sc. in 8–12 sites (80–120 MU) A/Dysport/20 MU/0.1 ml saline (high dose) sc. in 8–12 sites (160–240 MU)	Day, 7, 14, 21, 28	Pain severity by VAS†; quality of life by European Organization for Research and Treatment of Cancer surveys QLQ-C-30 and QLQ-H&N35‡	None	Two patients in high-dose group with neck weakness lasting up to 8 weeks	Low-dose group had significant pain reduction by VAS. Effect not seen in high dose group; low-dose group have trend toward improved quality of life and decreased functional pain (both nonsignificant)‡	Neuropathic pain resulting from modified radical cervical neck dissection; no placebo; open trial; study performed predominantly on male population (21 males, two females)	[34]

†Primary outcome measures; ‡Secondary outcome measures.
sc.: Subcutaneous; VAS: Visual analog scale.

Table 4. Botulinum toxin in carpal tunnel syndrome.

Study (year)	Class	Design	Cohort Size	Treatment (serotype/brand/dose)	Follow-up	Outcome	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Breuer *et al.* (2006)	I	Randomized, double-blind, placebo-controlled clinical trial BoNT-A vs NS injections	20	B/Myobloc® (Solstice Neurosciences, CA, USA)/2500 U divided over three hypothenar muscles	Week 1, 5, 9, 13	Pain intensity, pain interference with sleep, painful tingling	None	Two patients who received higher doses of BoNT-B experienced discomfort and weakness of injected fingers for 5–6 weeks	BoNT-B is not superior to placebo in CTS-related pain	Injection into hypothenar muscles	[35]
Tsai *et al.* (2006)	IV	Open-label prospective pilot study	5	A/Dysport® (Ipsen Pharma), 30 U intracarpally on each side of the carpal tunnel	Month 1, 2, 3	Pain severity by VAS, Conduction time by NCS	None	None	Three patients had a nonsignificant pain trend toward improvement at 3 months, no change in conduction time by NCS	Case series, no placebo	[36]

BoNT: Botulinum toxin; CTS: Carpal tunnel syndrome; NCS: Nerve conduction studies; NS: Normal saline; VAS: Visual analog scale.

were followed at weeks 2 and 4, but only those patients who received onabotulinumtoxinA were followed for another 20 weeks in an open-label phase. Results indicated that 87% of patients who received onabotulinumtoxinA injections experienced a significant ($p < 0.001$) reduction of >50% in VAS at weeks 2 and 4, an effect that continued during the open-label phase through week 16. By contrast, no patients who received placebo experienced a significant reduction in VAS at weeks 2 and 4. Sleep scores also improved ($p < 0.001$) at weeks 2 and 4 in patients who received onabotulinumtoxinA, remaining unchanged in the open-label phase. Sleep scores in patients who received placebo showed nonsignificant trends for improvement at week 2, as well at week 4 [20].

In summary, there are two class I studies [19,20] that show efficacy of BoNT in the management of postherpetic neuralgia **(Table 1)**. Therefore, there is established efficacy for BoNT for the management of postherpetic neuralgia pain based on level A evidence.

■ Trigeminal neuralgia

In a randomized, double-blind, placebo-controlled clinical trial performed by Wu *et al.* on 42 patients with refractory trigeminal neuralgia, the Chinese preparation of BoNT-A (Lanzhou Biological Products Institute, China) was injected intradermally and submucosally. Results indicate statistically significant improvement in all end points including pain severity by VAS, pain attack frequency, and patient's response to treatment by the patient global impression of change scale. A total of 75 U of the Lanzhou, China preparation of BoNT-A was injected in 15 points followed weekly for 12 weeks. Pain severity reduction reached significance at week 2 ($p < 0.05$), and pain attack decrease in frequency reached significance at week 1 ($p < 0.05$); both remained significant through the conclusion of the study. Five patients experienced transient facial asymmetry in the BoNT-A group, three patients experienced transient injection site edema [21].

Bohluli *et al.* published preliminary data of an uncontrolled, nonrandomized, open-label trial of 15 patients with a 6-month to 24-year history of refractory trigeminal neuralgia in which an unspecified preparation of BoNT-A was injected into trigger zones (50–100 U of BoNT-A at each trigger zone with an unspecified depth of injection) identified by patients and confirmed by

clinical examination and by response to lidocaine injection. Patients were evaluated at 1 week, 1 month and 6 months following injections. As compared with each patient's baseline levels prior to injection, pain severity and attack frequency were reduced at 1 week and 1 month in all patients ($p < 0.001$). Patient global assessment scale 6 months after injection showed improvement in all patients ($p < 0.001$). Complete eradication of pain was achieved in seven patients. Three patients experienced transient partial facial paresis [22].

In an open-label trial of 8 patients with refractory trigeminal neuralgia, Turk *et al.* performed injections of 100 U of onabotulinumtoxinA divided over two sites above and below the zygomatic arch. All patients had significant reductions in pain severity by VAS ($p = 0.011$) and attack frequency ($p = 0.012$) at 1 week, 2 months and 6 months with reported relief beginning within hours to days postinjection. The only side effects included one patient with transient dysesthesia and another with transient chewing difficulty. Baseline mean levels of pain severity and attack frequency were moderate prior to injection, and mean duration of disease was 1.6 ± 1.1 years [23].

Piovesan *et al.* reported an open-label pilot study of 13 patients with refractory trigeminal neuralgia in which all patients experienced significant reductions in pain severity by VAS and pain surface area 10, 20, 30 and 60 days after injection of an unspecified preparation of BoNT-A ($p < 0.05$). Varying doses of BoNT-A were injected transcutaneously in a grid pattern within the painful affected areas, with the dose calculated for each patient based on the affected area (mean therapeutic coefficient for all patients: 3.22 U/cm^2). The effects were seen by day 10 in all patients, with a peak in benefit at day 20. The benefit allowed four patients to completely stop all preventive meds at day 60, while the others reduced consumption by more than 50%. While there were no major side effects, three patients experienced facial asymmetry and another experienced ptosis. Unfortunately, it is not known how long the therapeutic effect remained, since the patients were followed for only 60 days after injection, prior to termination of benefit in all patients [24].

Of 12 patients with refractory trigeminal neuralgia injected with onabotulinumtoxinA in an open-label case series published by Zuniga *et al.*, ten experienced a reduction in pain severity by

Table 5. Botulinum toxin for diabetic polyneuropathy.

Study (year)	Class	Design	Cohort Size	Treatment (serotype/brand/dose)	Follow-up	Outcome	Drop outs	Adverse events	Results/effect size	Ref.
Yuan *et al.* (2009)	II	Randomized, double-blind, placebo-controlled, crossover trial; subjects received injections of other agent after 12 weeks	20	A/Botox® (Allergan, CA, USA)/50 U intradermally over 12 sites in dorsum of foot in a grid pattern	Week 1, 4, 8, 12	Pain severity reduction by VAS within 12 weeks†; Chinese version of Pittsburgh Sleep Quality Index; Short Form 36 QOL questionnaire‡	2	One patient experienced mild local skin infection that resolved with antibiotics	Significant reductions in VAS in BoNT-A group; 44.4% of BoNT-A patient experienced good responsive (VAS decrease ≥3) vs none in placebo group†; significant improvement in sleep for BoNT-A group only at week 4‡; no significant differences in QOL between groups by Short Form 36 QOL questionnaire	[37]

†Primary outcome; ‡Secondary outcome.
QOL: Quality of life; VAS: Visual analog scale.

Table 6. Botulinum toxin in complex regional pain syndrome.

Study (year)	Class	Design	Cohort size	Treatment (serotype/ brand/dose)	Follow-up	Outcome	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Safarpour *et al.* (2010)	III	Randomized, prospective, double-blind, placebo-controlled clinical trial	14	A/Botox® (Allergan, CA, USA)/5 U per site intradermally and sc. in 10–40 sites	Week 3, 8	Pain severity by Brief pain inventory, pain days by PIQ, Quantitative sensory test†; activities of daily living by PIQ, pain severity by McGill pain questionnaire, sleep interference by brief pain inventory, patient satisfaction scale‡	None	Intolerable injection pain	No pain relief at 3 or 8 weeks from BoNT-A, intolerable injection pain; one patient with postherpetic neuralgia experienced significant 90% pain relief at 2 months	–	[38]
Carroll *et al.* (2009)	III	Randomized, prospective, double-blind, controlled, crossover study of lumbar sympathetic block with bupivacaine vs lumbar sympathetic block with bupivacaine and BoNT-A	9	A/unspecified preparation/75 U mixed with bupivacaine administered in lumbar sympathetic block	Daily VAS diary until pain returned to baseline or 1 month	Pain severity by VAS, duration of pain relief	2	Transient nausea and emesis in one patient	Significant prolongation of pain relief in BoNT/bupivacaine group compared with bupivacaine alone (71 vs <10 days)	Unspecified BoNT-A preparation	[39]
Kharkar 2011	IV	N/A	37	A/unspecified preparation/ 10–20 U per muscle, total 100 U	Week 4	Pain severity by Likert scale	None	One patient was transient neck drop	97% with significant pain relief, average of 43% decrease in local pain scores 4 weeks after injection compared with baseline	Unspecified BoNT-A preparation; case series, no placebo	[40]
Birthi *et al.* (2012)	IV	N/A	1	A/unspecified preparation/ 100 U sc. divided over 20 sites	Week 1, 2, 3, 4, 5, 6, 7, 8, 12	Pain severity by McGill Pain Questionnaire, ROM by examination	N/A	None	Reduction in pain by day 3 lasting up to 3 months, decrease in opioid requirements, 15° improvement in ROM at wrist, 30° improvement in ROM at digits, improvement in ADL	Unspecified BoNT-A preparation, case report	[41]

†Primary outcome; ‡Secondary outcome.

ADL: Activities of daily living; BoNT: Botulinum toxin; N/A: Not applicable; PIQ: Clinical Pain Impact Questionnaire; ROM: Range of motion; sc.: Subcutaneous; VAS: Visual analog scale.

VAS. Injections of 20–50 U were divided into trigger zones. One patient experienced the minor side effect of transient facial asymmetry [25].

Borodic and Acquadro performed an open-label pilot study on 44 patients with chronic facial pain to evaluate the response to onabotulinumtoxinA injection [26]. The patients included in the study had a variety of medical disorders including idiopathic trigeminal neuralgia, temporomandibular joint syndrome, postsurgical chronic pain syndromes and chronic essential headache. In assessing the 11 subjects with refractory trigeminal neuralgia, eight of them experienced >50% reduction in pain frequency or intensity following injection of onabotulinumtoxinA (30–50 U at a depth of 1–3 mm). Minor side effects including transient facial asymmetry and weakness were observed in subjects [26].

In summary, only one class I study [21] (in addition to multiple case reports and small case series [22–32]) demonstrated therapeutic benefit of BoNT injection in trigeminal neuralgia pain **(Table 2)**. Therefore, BoNT is probably effective for the management of trigeminal neuralgia based on level B evidence.

■ Post-traumatic neuralgia

Ranoux *et al.* performed a randomized, placebo-controlled, double-blind class I study of 29 patients with neuropathic pain (25 with post-traumatic/postoperative neuropathic pain; four with postherpetic neuralgia). The investigators injected either normal saline or onabotulinumtoxinA (5 U at each site spaced 1.5 cm apart in a grid pattern within the area of allodynia, averaging 20 injections per person) intradermally and followed-up 4, 12 and 24 weeks postinjection to determine the effect of onabotulinumtoxinA on weekly average pain amongst other measures. Patients in the onabotulinumtoxinA group experienced significant reductions in weekly average pain levels as compared with placebo beginning at week 2 ($p = 0.025$), with an effect persisting for various time points until week 14 ($p = 0.03$). Compared with the placebo, onabotulinumtoxinA also produced a reduction in allodynia to brush and cold; improvement in average pain intensity; improvement in global pain relief; improvement of three neuropathic symptoms including burning, paroxysmal pain, and allodynia; along with decreased pain paroxysms. Additionally onabotulinumtoxinA improved general activity, mood and anxiety scores [33].

Table 7. Botulinum toxin for phantom limb and stump pain.

Study (year)	Class	Design	Cohort size	Treatment (serotype/brand/dose)	Follow-up	Outcome	Drop outs	Adverse events	Results/effect size	Ref.
Wu *et al.* (2012)	III	Prospective, randomized, double-blinded pilot study	14	A/Botox® (Allergan, CA, USA)/50 U per site, total 250–300 U vs lidocaine/depomedrol combination	Monthly (x6 months)	VAS, changes in pressure pain tolerance as determined by pressure algometer	None	No acute side effects	Both groups had immediate improvement of RLP and pain tolerance lasting 6 months; no statistical differences in RLP and pain tolerance between groups; no improvement of PLP in either group	[42]
Jin *et al.* (2009)	IV	Case series, BoNT-A injection into painful stumps	3	A/Dysport® (Ipsen Pharma)/ 500 U under EMG guidance into muscle	N/A	CGI based on 0–3 scale (0 = no effect, 3 = marked improvement), VAS, evaluated gait unsteadiness	None	None	All three patients experienced significant pain relief, which improved prosthesis tolerance and allowed for a reduction in pain meds; effect lasted up to 11 weeks	[43]

BoNT: Botulinum toxin; CGI: Global Clinical Improvement; EMG: Electromyography; N/A: Not applicable; PLP: Phantom limb pain; RLP: Residual limb pain; VAS: Visual analog scale.

Table 8. Botulinum toxin for occipital neuralgia.

Study (year)	Class	Design	Cohort size	Treatment (serotype/ brand/dose)	Follow-up	Outcome	Drop outs	Adverse events	Results/effect size	Comments	Ref.
Kapural *et al.* (2007)	IV	Retrospective, open-label case series of occipital nerve block with BoNT-A vs 0.5% bupivacaine	6	A/Botox® (Allergan, CA, USA)/50 U per occipital nerve block	Week 4	Pain severity by VAS, opiate use, PDI	None	Not mentioned	Decreased VAS in both groups; pain relief lasted 16 weeks in BoNT-A group vs 2 weeks in bupivacaine group. Improved PDI; variable need for opiates	Retrospective data collection, no true placebo	[44]
Taylor *et al.* (2008)	IV	Prospective, open-label case series of occipital nerve block with BoNT-A	6	A/Botox/50 U per occipital nerve block	Week 6, 12	Pain severity by VAS†; headache-free days, medication use, quality of life measures‡	None (partial data only on two patients)	Not mentioned	Improved sharp/shooting and pins/needles pain during reaching significance at several time points; no significant reduction in pain medication use; headache-specific quality of life improved between 6 and 12 weeks	No placebo	[45]

†Primary outcome; ‡Secondary outcome.
BoNT: Botulinum toxin; PDI: Pain Disability Index; VAS: Visual analog scale.

In a Phase II prospective, randomized, open-label clinical trial of 23 patients who developed neuropathic pain following surgical neck dissection in the distribution of the superficial cervical plexus, Wittekindt *et al.* found that low-dose (10 MU/0.1 ml saline) subcutaneous injections of abobotulinumtoxinA were more effective at reducing pain severity by VAS than high-dose (20 MU/0.1 ml saline) subcutaneous injections in the target area with injections separated by 1.5 cm. Patients in the low-dose group received a total of 80–120 MU, while patients in the high-dose group received a total of 160–240 MU. The decrease in pain was significant in the low-dose group for VAS levels obtained on day 28 as compared with baseline VAS levels. Additionally, in the low-dose group there was a trend toward improved quality of life and a decrease in a functional pain scale, although these measures did not reach statistical significance. The high-dose group was less effective at reducing pain than the low-dose group and had unwanted side effects of neck weakness in two patients lasting up to 8 weeks [34].

In summary, there is one class I study [33] and one class IV study [34], which demonstrates that BoNT is probably effective (level B evidence) in the management of post-traumatic neuralgia **(Table 3)**.

■ Carpal tunnel syndrome:

Breuer *et al.* performed a randomized, double-blind, placebo-controlled clinical trial of 20 patients with nerve conduction studies-confirmed carpal tunnel syndrome. The patients were randomized to receive injections of either rimabotulinumtoxinB or normal saline into hypothenar muscles to determine if rimabotulinumtoxinB injection had an effect on palmar pain and discomfort. Patients were monitored by weekly telephone calls up to 13 weeks to determine pain severity, effect on sleep, and quality of life by West Haven-Yale Multidimensional Pain Inventory. Additionally, patients presented in follow-up at weeks 1, 5, 9 and 13. The first two subjects received higher doses of rimabotulinumtoxinB (5000 and 7500 U) with the adverse effects of weakness and discomfort in the fourth and fifth fingers that lasted 5–6 weeks and required unblinding. The remaining patients in the study therefore received lower doses of rimabotulinumtoxinB (2500 U total over three hypothenar muscles) and did not experience these adverse effects.

Table 9. Botulinum toxin for upper limb spasticity in adults.

Study (year)	Class	Design	Cohort size	Treatment (serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures	Results	Adverse events	Ref.
Bakheit *et al.* (2000)	I	Multicenter, randomized, double-blind, placebo-controlled, dose ranging study	82	A/Dysport® (Ipsen Pharma)/500, 1000, 1500 U (four arms; placebo)	Anatomic landmarks	16 weeks	Modified Ashworth† Barthel index‡ Hygiene or dressing Rivermead motor	+ 0 0 0	No significant difference between the study arms	[46]
Bakheit *et al.* (2001)	I	Multicenter, randomized, double-blind, placebo-controlled	59	A/Dysport/1000 U (two arms; placebo)	Anatomic landmarks	16 weeks	Modified Ashworth Scale† Range of motion‡ Barthel index Pain score Goal attainment Patient's evaluation of benefit Physician rating of benefit	+ 0 0 0 0 + +	No significant difference between study groups	[47]
Bhakta *et al.* (2000)	I	Single-center, randomized, double-blind, placebo-controlled	40	A/Dysport/1000 U (two arms; placebo)	Anatomical landmarks	12 weeks	At 6 weeks: Participant disability scale† Caregiver disability scale Modified Ashworth Scale‡ Passive range of motion Arm pain Grip strength	 + + + 0 0 Decreased grip strength in BoNT group	Self-limiting pain in 10% of BoNT group	[60]
Brashear *et al.* (2002)	I	Multicenter, randomized, double-blind, placebo-controlled	126	A/Botox® (Allergan, CA, USA)/200–240 U (two arms; placebo)	Not specified	12 weeks	Disability score at 6 weeks† Ashworth‡ Physician's global assessment scale Patient's or caregiver's global assessment scale	+ + + +	No significant differences between study groups	[58]

†Primary outcome; ‡Secondary outcome.

+: Significant difference between botulinum toxin group and control group; 0: No significant difference between botulinum toxin group and control group; BoNT: Botulinum toxin; EMG: Electromyography; SF36: Short Form 36 Quality of Life Questionaire; VAS: Visual analog scale.

Table 9. Botulinum toxin for upper limb spasticity in adults (cont.).

Study (year)	Class	Design	Cohort size	Treatment (serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures	Results	Adverse events	Ref.
Brashear *et al.* (2004)	I	Single-center, randomized, double-blind, placebo-controlled	15	B/Myobloc® (Solstice Neurosciences, CA, USA)/10,000 U (two arms; placebo)	Stimulation technique	16 weeks	Ashworth Scale (at 2 weeks)† Physician/participant global assessment‡ Pain	+ 0 0	Dry mouth in 8/9 BoNT treated participants vs 1/5 in the placebo group	[57]
Childers *et al.* (2004)	I	Multicenter, randomized, double-blind, placebo-controlled	91	A/Botox/90, 180 and 320 U (four arms; placebo)	EMG guidance	6 months	Modified Ashworth Scale (wrist)† Modified Ashworth Scale (elbow and fingers)‡ Physician/participant global assessment Pain SF36 FIM	+ (dose dependent) + (dose dependent) 0 0 0 0	Self-limiting arm pain and hematoma at injection site	[53]
Hesse *et al.* (1998)	I	Single-center, randomized, double-blind, placebo-controlled	24	A/Dysport/1000 U (four arms; BoNT-A plus electrical simulator; BoNT-A alone; placebo plus electrical stimulator; placebo alone)	EMG guidance	12 weeks	Modified Ashworth Scale† Limb position at rest‡ Hygiene	0 0 +	None	[62]
Kaji *et al.* (2010)	I	Multicenter, randomized, double-blind, placebo-controlled	109	A/Botox/low dose: 120–150 U; high dose: 200–240 U (three arms; placebo)	EMG guidance	12 weeks	Modified Ashworth Scale Disability Assessment Scale	+ (high dose) + (high dose)	No significant difference between groups	[49]
Kanovsky *et al.* (2009)	I	Multicenter, randomized, double-blind, placebo-controlled,	148	A/Xeomin® (Merz, NC, USA)/median: 320 U (two arms; placebo)	EMG guidance	20 weeks	Disability Assessment Scale† Ashworth Scale‡ Global assessment of efficacy Carer Burden Scale	+ + + +	No difference between study groups	[50]
Lam *et al.* (2012)	I	Multicenter, randomized, double-blind, placebo-controlled	55	A/Dysport/up to 1000 U (one arm; placebo)	Not specified	24 weeks	Carer Burden Scale† Goal attainment scale‡ Modified Ashworth Scale Passive range of motion Pain	+ + + + 0	No significant difference between groups	[52]

†Primary outcome; ‡Secondary outcome.

+: Significant difference between botulinum toxin group and control group; 0: No significant difference between botulinum toxin group and control group; BoNT: Botulinum toxin; EMG: Electromyography; SF36: Short Form 36 Quality of Life Questionaire; VAS: Visual analog scale.

Table 9. Botulinum toxin for upper limb spasticity in adults (cont.).

Study (year)	Class	Design	Cohort size	Treatment (serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures	Results	Adverse events	Ref.
Marco *et al.* (2007)	I	Single-center, randomized, double-blind, placebo-controlled	31	A/Dysport/500 U (two arms; placebo) Both groups received transcutaneous electrical nerve stimulation for 6 weeks after infiltration	EMG guidance	6 months	VAS for pain† Modified Ashworth Scale‡ Shoulder range of motion	+ 0 0	No significant adverse effects in treatment group	[61]
McCrory *et al.* (2009)	I	Multicenter, randomized, double-blind, placebo-controlled	96	A/Dysport/750–1000 U (two arms; placebo)	EMG guidance	24 weeks	Assessment of Quality of Life Scale† Goal attainment scaling‡ Pain Mood Global benefit Modified Ashworth Scale Disability Carer burden	0 + 0 0 + + 0 0	No difference between groups	[51]
Richardson *et al.* (2000)	I	Single-center, randomized, double-blind, placebo-controlled	32	A/Botox/mean dose: 183 U (two arms; placebo)	EMG guidance	12 weeks	Upper and lower limb spasticity: Modified Ashworth Scale Passive range of motion Subjective rating of problem severity	 + + +	Pain at injection site (n = 4)	[54]
Rosales *et al.* (2012)	I	Multicenter, randomized, double-blind, placebo-controlled	163	A/Dysport/500 U (two arms; placebo)	Not specified	24 weeks	Modified Ashworth Score† Functional Motor Assessment Scale‡ Global pain scale Goniometry	+ 0 + +	No significant difference between groups	[48]
Shaw *et al.* (2011)	I	Multicenter, randomized, controlled, outcome assessment blinded	333	A/Dysport/100–200 U (two arms; therapy only vs 100–200 U plus therapy)	Not specified	12 months	Action Research Arm Test at 1 month† Muscle tone‡ Upper limb strength Pain Basic arm functional tasks	0 + (at 1 month) + (at 3 months) + (at 12 months) + (at 1, 3, and 12 months)	Higher incidence of general malaise/ flu-like/cold symptoms in the BoNT group	[63]
Simpson *et al.* (1996)	I	Multicenter, randomized, double-blind, placebo-controlled	39	A/Botox; dose escalation (75, 100 and 300 U) vs placebo	EMG guidance	16 weeks	Ashworth Scale† Physician/participant global assessment‡ FIM Caregiver dependency Fugl-Meyer	+ + 0 0 0	No significant difference between the groups	[59]

†Primary outcome; ‡Secondary outcome.

+: Significant difference between botulinum toxin group and control group; 0: No significant difference between botulinum toxin group and control group; BoNT: Botulinum toxin; EMG: Electromyography; SF36: Short Form 36 Quality of Life Questionaire; VAS: Visual analog scale.

Table 9. Botulinum toxin for upper limb spasticity in adults (cont.).

Study (year)	Class	Design	Cohort size	Treatment (serotype/ brand/dose)	Targeting technique	Follow-up	Outcome measures	Results	Adverse events	Ref.
Smith *et al.* (2000)	I	Single-center, randomized, double-blind, placebo-controlled	21	A/Dysport; four arms; placebo (500, 1000 1500 U); combining all three BoNT groups for statistical analysis	Not specified	12 weeks	At 6 weeks: Modified Ashworth Scale† Passive range of motion Frenchay Arm Test‡ Upper body dressing time Patient global assessment	 + + (wrist and fingers); 0 for elbow 0 0 +	Flu-like symptoms for 2 days after injection in one patient	[55]
Suputtitada *et al.* (2005)	I	Single-center, randomized, ouble-blind, placebo-controlled, dose-ranging	50	A/Dysport; four arms; placebo (350, 500 and 1000 U)	EMG guidance	6 months	Modified Ashworth Scale† Action Research Arm Test‡ Barthel Index Pain	+ (in all groups) + (in 500 U group) + (in 500 U group) + (in all groups)	–	[56]

†Primary outcome; ‡Secondary outcome.
+: Significant difference between botulinum toxin group and control group; 0: No significant difference between botulinum toxin group and control group; BoNT: Botulinum toxin; EMG: Electromyography; SF36: Short Form 36 Quality of Life Questionaire; VAS: Visual analog scale.

The authors found no benefit from injection of rimabotulinumtoxinB on pain, sleep, or quality of life compared with the placebo [35].

In a smaller open-label series of five women with a history of carpal tunnel syndrome, Tsai *et al.* investigated the effect of abobotulinumtoxinA on pain by VAS and conduction velocities by nerve conduction studies. The investigators injected a total of 60 U intracarpally and followed the patients monthly for 3 months. [36] The patients experienced no weakness, unlike that seen in the study by Breuer *et al.*, probably since the abobotulinumtoxinA was not injected into the muscle. While there was a trend toward pain improvement in three patients, the finding was not significant. Additionally, there were no changes in nerve conduction velocities by nerve conduction studies following abobotulinumtoxinA injection.

Based on one class I study [35] and one class IV study [36] that showed no significant effect on pain following BoNT injection for carpal tunnel syndrome pain, the use of BoNT is probably not effective (level B evidence) **(Table 4)**.

■ Diabetic polyneuropathy

Yuan *et al.* performed a randomized, placebo-controlled, double-blind crossover trial in which 20 patients with at least 3 years of diabetic polyneuropathy involving the feet (18 of whom completed the study) received injections of saline or onabotulinumtoxinA intradermally in the dorsum of their feet, then 12 weeks after injection received the other therapy applied in the same distribution. The investigators measured VAS in addition to measures of sleep quality by a Chinese version of the Pittsburgh Sleep Quality Index as well as the quality of life questionnaire SF-36. A significant decrease in pain severity by VAS was observed in response to onabotulinumtoxinA injections compared with the placebo at 4 weeks ($p = 0.014$), 8 weeks ($p = 0.039$) and 12 weeks ($p = 0.024$) postinjection. Sleep quality improved comparing the onabotulinumtoxinA and placebo groups only at 4 weeks postinjection ($p < 0.05$). There was no significant difference in quality of life between the two groups [37].

Based on one class II study [37] demonstrating benefit from BoNT on neuropathic pain in diabetic polyneuropathy, the use of BoNT is possibly effective (level C evidence) **(Table 5)**.

■ Complex regional pain syndrome

Safarpour *et al.* performed a randomized, prospective, double-blind, placebo-controlled

clinical trial of eight patients with CRPS (six additional patients underwent an open-label protocol) which revealed that onabotulinumtoxinA injections had no improvement in pain and were very poorly tolerated owing to injection pain [38].

To determine if BoNT-A increases the duration of analgesia experienced after lumbar sympathetic block, Carroll *et al.* performed a randomized, double-blind, controlled crossover study on nine patients with CRPS and found a significant prolongation of analgesia (71 days vs <10 days; $p < 0.02$) when bupivacaine lumbar sympathetic blocks are combined with 75 U of an unspecified form of BoNT-A. One patient experienced transient nausea and vomiting [39].

In an uncontrolled, retrospective chart review of 37 patients with CRPS who received intramuscular injections of BoNT-A totalling 100 U, Kharkar *et al.* demonstrated a decrease in pain from baseline by 2 or more points in 97% of subjects 4 weeks postinjection, with an average reduction in pain scores by 43% ($p < 0.001$). While no serious side effects were observed, one patient experienced neck drop lasting 2 weeks which required use of a neck brace [40].

Based on one class III study showing negative results [38] in conflict with 1 class III study [39] and two class IV studies [40,41] showing positive results, there is level U (insufficient) evidence for use of BoNT in the management of pain associated with CRPS **(Table 6)**.

Phantom limb & stump pain

Wu *et al.* performed a prospective, randomized, double-blind pilot study of 14 amputees with intractable residual limb pain and/or phantom limb pain in which patients received intramuscular and cutaneous/subcutaneous injections of either onabotulinumtoxinA or a combination of lidocaine/depomedrol. The patients were followed monthly for a total of 6 months. Outcomes measured were pain severity by VAS and changes in pressure pain tolerance as determined by a pressure algometer. While residual limb pain improved in both groups for up to 6 months, there was no improvement in phantom limb pain for either group observed. There were no side effects listed [42].

Jin *et al.* injected abobotulinumtoxinA under EMG guidance into the stumps of 3 amputees with phantom limb pain in a small case series and found that all patients received marked pain relief by VAS with improved tolerance of their prosthesis for up to 11 weeks without side effects [43].

Based on conflicting data from one class III study [42] and one class IV study [43], there is level U insufficient evidence for the use of BoNT in the management of phantom limb pain **(Table 7)**.

Occipital neuralgia

Kapural *et al.* performed an open-label retrospective overview of six patients with occipital neuralgia who received occipital nerve blocks with onabotulinumtoxinA. The same patients had experienced short-term pain relief lasting up to 2 weeks following a diagnostic occipital nerve block with the local anesthetic 0.5% bupivacaine. The investigators then performed the occipital nerve block with 50 U of subcutaneous onabotulinumtoxinA for unilateral occipital neuralgia (otherwise 100 U for bilateral occipital neuralgia) on those patients and found that they experienced longer-lasting pain relief (lasting more than 4 months in five patients), with improvement in pain disability index [44].

Taylor *et al.* performed an open-label trial of six patients to see if onabotulinumtoxinA injected in an occipital nerve block provided pain relief of their chronic occipital neuralgia. 50 U of onabotulinumtoxinA was injected per affected side. The patients kept a daily pain log according to headache type (dull/aching, sharp/shooting, pins/needles), completed surveys assessing their quality of life, and reported daily pain medication usage for 12 weeks postinjection. Of the pain types identified, the investigators found that both the pins/needles and sharp/shooting pain were significantly improved from baseline at various time points during the study. The pins/needles pain improvement reached statistical significance from baseline at weeks 3–6, while the sharp/shooting pain improvement reached statistical significance from baseline at weeks 2–3 and 7–12. The dull/aching pain did not improve significantly following onabotulinumtoxinA injection. In spite of the improvement in various pain types, no patients experienced any headache-free days following injections. There was no change in pain medication required by subjects following injections. Some quality of life measures showed improvement, but many showed no change. The trial was performed without placebo [45].

Table 10. Botulinum toxin for lower limb spasticity in adults.

Study (year)	Class	Design	Cohort Size	Treatment (serotype/brand/dose)	Targeting technique	Follow-up	Outcome measures	Results	Adverse events	Comments	Ref.
Dunne *et al.* (2012)	I	Multicenter, randomized, double-blind, placebo-controlled	85	A/Botox® (Allergan, CA, USA)/200 and 300 U (three arms; placebo; botox groups were pooled for data analysis	EMG guidance	12 weeks	Ashworth† Spasm frequency‡ Pain Gait quality Active dorsiflexion	0 + + + +	No significant difference between the groups	Subjects with Ashworth >3 at baseline demonstrated a significant decrease in hypertonia compared with placebo group in subgroup analysis	[70]
Hyman *et al.* (2000)	I	Multicenter, randomized, double-blind, placebo-controlled	74	A/Dysport® (Ipsen Pharma)/500, 1000 and 1500 U (four arms; placebo)	Anatomic landmarks	4 weeks: primary analysis point 12-week follow-up	Passive range of hip† abduction Muscle tone‡ Hygiene Pain Global rating	+ + 0 0 0	Muscle weakness, constipation and nausea more common in 1500 U Dysport group	–	[67]
Maanum *et al.* (2011)	I	Single-center, randomized, double-blind, placebo-controlled	66	A/Botox/dose specified for each muscle (two arms; placebo)	EMG guidance	16 weeks	Kinematics† Health-related quality of life Muscle stiffness/spasticity‡ Timed up and go 6-min walk test Global scale of perceived effect	0 0 + 0 0 +	No difference between study groups	–	[68]
Pittock *et al.* (2003)	I	Multicenter, double-blind, placebo-controlled, dose-ranging	234	A/Dysport/500, 1000 and 1500 U (four arms; placebo)	Anatomic landmarks	12 weeks	2-min walking distance† Modified Ashworth Scale (ankle) Pain Global score Need for aids Active and passive range of motion (ankle) Rivermead Motor Assessment	0 + (dose dependent) + (dose dependent) 0 + 0 0	–	–	[69]

†Primary outcome; ‡Secondary outcome.
+: Significant difference between botulinum toxin group and control group; 0: No significant difference between botulinum toxin group and control group; EMG: Electromyography.

Table 10. Botulinum toxin for lower limb spasticity in adults (cont.).

Study (year)	Class	Design	Cohort Size	Treatment (serotype/brand/dose)	Targeting technique	Follow-up	Outcome measures	Results	Adverse events	Comments	Ref.
Kaji *et al.* (2010)	I	Multicenter, randomized, double-blind, placebo-controlled	120	A/Botox/300 U (two arms; placebo)	EMG guidance	12 weeks	Modified Ashworth Scale[†] Clinician global impression[‡] Patient global impression Gait pattern Gait speed	+ + 0 0 0	No significant difference between groups	–	[66]
Richardson *et al.* (2000)	I	Single-center, randomized, double-blind, placebo-controlled	32	A/Botox/mean dose: 183 U (two arms; placebo)	EMG guidance		Upper and lower limb spasticity: Modified Ashworth Scale Passive range of motion Subjective rating	 + + +	Pain at injection site (n = 4)	–	[54]

[†]Primary outcome; [‡]Secondary outcome.
+: Significant difference between botulinum toxin group and control group; 0: No significant difference between botulinum toxin group and control group; EMG: Electromyography.

Based on only two class IV studies [44,45], there is level U (insufficient) evidence for use of BoNT in the management of occipital neuralgia (Table 8).

Adult spasticity

The following section reviews randomized controlled double-blind trials investigating the clinical effects of BoNT on upper and lower extremity spasticity in adults (Tables 9 & 10).

■ Adult spasticity in the upper extremities:

The majority of clinical trials have shown that BoNT decreases muscle tone [46–60], leading to improved range of motion in some studies [52,54,55] but not others [47,60,61]. Only two relatively small studies with less than 32 participants each found no effect of BoNT on muscle tone [61,62]. All studies except one [51] demonstrated decreased disability scores as reported by patients and caregivers [49,50,60]. Both patients and physicians perceived an overall benefit of BoNT, which was statistically significant in all [47,50,51,55,58,59] but two studies [53,57]. However, this perceived overall benefit and decrease in disability is not necessarily associated with improved performance on arm function scales, as most studies do not show functional gain [46–48,51,55]. Only one study shows functional gain [56], while another study has mixed results with improvement in some but not all functional tests [63]. Similarly, the results of studies using activities of daily living such as dressing and hygiene as functional outcome measures are conflicting, with some studies showing benefit in patients treated with BoNT [56,62], whereas others have not found a difference between treatment and placebo groups [46,47,55]. Outcomes in terms of caregiver burden are equally discrepant between studies, with some trials showing decreased caregiver burden [50,52], whereas others do not [51,59]. Several authors have reported a reduction in pain scores following BoNT injection [48,56,61,63], but this finding has not been consistently replicated [47,51–53,57].

Two recent randomized controlled clinical trials compared BoNT to other treatments for upper extremity spasticity. One study showed that BoNT is more effective than tizanidine in decreasing muscle tone and disability scores [64]. A small study of 29 stroke patients with shoulder pain, which compared BoNT to intra-articular injection of triamcinolone, found a trend to superiority of BoNT in terms of pain control and improvement of range of motion [65].

■ Adult spasticity in the lower extremities

BoNT has been shown to be effective at decreasing muscle tone in all [54,66–69] but one study [70]. Similarly, two studies found improvement in pain [69,70] and increasing range of motion [54,67], respectively, but others found no difference between treatment and placebo groups in measures of pain [67] and range of motion [69] in adults with lower extremity spasticity. The only study assessing active joint movement, spasm frequency and gait quality found a significant benefit in participants treated with BoNT as opposed to those receiving placebo. Patient or physician reported overall perceived benefit showed discrepancies, with some studies suggesting a benefit of BoNT [54,66,68] whereas others did not [67,69]. Several studies using different gait assessments as a functional outcome measure did not reveal a significant difference between BoNT and placebo groups [66,68,69], and there was no benefit in terms of personal hygiene [67]. One small study investigated the benefit of adding kinesiotaping to BoNT therapy in 20 patients with spastic equinus foot, and found that passive range of motion was improved in patients who were treated with kinesiotaping as opposed to those who had received a sham taping procedure [71].

Conclusion & future perspective

In summary, the use of BoNT in neuropathic pain conditions has become more widely considered based on evidence of BoNT's effect in pain modulation. However, there exists a need for more class I studies on BoNT use in different types of neuropathic pain. Of the neuropathic pain conditions considered in this review, the following evidence has been designated: there is level A evidence for established efficacy of BoNT injection in postherpetic neuralgia; level B evidence for probable efficacy of BoNT injection in trigeminal neuralgia and post-traumatic neuralgia; level B evidence for probable lack of efficacy of BoNT injection in carpal tunnel syndrome; level C evidence for possible efficacy of BoNT injection in diabetic polyneuropathy; and level U evidence for BoNT injection in CRPS, phantom limb and stump pain, and occipital neuralgia. An important practical consideration is the feasibility and acceptability

of multiple site injections for the treatment of neuropathic pain. There is also the concern of unwanted neuromuscular side effects, especially weakness. Next-generation toxins with selective afferent effects are under development.

BoNT is a safe and effective treatment for spasticity in adults (Level A evidence). The main benefit of BoNT treatment is decreased muscle tone, which may be associated with decreased disability, pain and caregiver burden. More studies are needed to assess long-term functional outcomes, the potential benefit of different injection techniques such as ultrasound or electrophysiological-guided injection, as well as the role of adjunct nonpharmacologic therapies in improving patient outcomes.

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