# Chapter 3
# Neuropathic Pain (NP)

**Abstract** Neuropathic pain (NP) is a common form of human pain, often poorly responsive to analgesic medications. This chapter discusses the pathophysiology and conventional treatment of common categories of neuropathic pain and reviews the literature on botulinum neurotoxin (BoNT) efficacy in neuropathic pain. The level of efficacy for BoNT treatment in each category is defined according to the published guidelines of the American Academy of Neurology. The data on type A toxin (mostly onabotulinumtoxinA, onaA) indicates efficacy in postherpetic neuralgia and probable efficacy in post-traumatic neuralgia, and painful diabetic neuropathy. Retrospective studies and anecdotal observations suggest efficacy in residual limb pain of amputees, complex regional pain syndrome, and chemotherapy-induced allodynia. Controlled studies are necessary to assess the efficacy of BoNTs in these conditions. Much remains to be learned about the most effective dosage and technique of injection, optimum dilutions, and differences among BoNTs in the treatment of neuropathic pain.

**Keywords** Botulinum toxin • Botulinum neurotoxin • Neuropathic pain • Pain • Allodynia • Postherpetic neuralgia • Post-traumatic neuralgia • Diabetic neuropathy • Complex regional pain syndrome • Phantom pain • Residual pain

## Introduction

Neuropathic pain (NP) is defined as a pain caused by lesion or disease of the somatosensory system (Treede 2012). The site of disturbance or damage can be peripheral (peripheral nerve, plexus, or root) or central (spinal cord, brain stem, or thalamus). Typically, the pain has a burning, jabbing, and searing quality. Skin areas of allodynia (touch perceived as pain), hyperalgesia (enhanced pain after exposure to painful stimuli), and hyperesthesia or dysesthesia (enhanced or altered sensations to touch) are common.

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**Electronic supplementary material** The online version of this chapter (10.1007/978-1-4939-2501-8_3) contains supplementary material, which is available to authorized users.



B. Jabbari, *Botulinum Toxin Treatment of Pain Disorders*,
DOI 10.1007/978-1-4939-2501-8_3

The pathophysiology of neuropathic pain is yet to be fully elucidated; the peripheral neuropathic pain (PNP) is currently believed to result from damage to peripheral nervous system with irritation of nerve endings and accumulation of nociceptive transmitters and modulators (substance P, glutamate, bradykinin, calcitonin gene-related peptide, and others). Accumulation of these agents produces local inflammation. Together, these two phenomena lower the sensory threshold of peripheral nerve endings to nociceptive stimuli (peripheral sensitization). Peripheral sensitization increases the number of nociceptive volleys into the spinal cord and leads to sensitization of sensory spinal cord neurons (central sensitization). The interplay between peripheral and central sensitization contributes to pain chronicity (Aoki and Francis 2011).

A number of mechanisms are now considered contributors to neuropathic pain (Table 3.1). Modifying these mechanisms is the basis of treatment strategies for NP treatment.

OnabotulinumtoxinA (onaA) has shown the potential to influence neuropathic pain in animals through a number of mechanisms: blocking the release of pain mediators from peripheral terminals and from dorsal root ganglia (Meng et al. 2007; Lucioni et al. 2008), decreasing local inflammation around nerve terminals (Cui et al. 2004), inhibiting sodium channels in peripheral and centred nervous system (Shin et al. 2012) discharge of muscle spindles (Filippi et al. 1993), and decreasing sympathetic transmission (Rand and Whaler 1965). The muscle spindle discharge can enhance central sensitization; increased sympathetic activity can maintain pain. The details of BoNTs' effects (particularly onaA) on experimental pain of animals and healthy human subjects are presented in Chap. 2.

Five examples of peripheral neuropathic pain (PNP) for which prospective and controlled data are available on BoNT efficacy are presented in this chapter. These include postherpetic neuralgia, post-traumatic neuralgia, painful diabetic neuropathy, complex regional pain syndrome, residual limb pain, and phantom pain. Case reports and videotapes are provided from the author's experience.

In this chapter and throughout the book, the level of efficacy for BoNTs is defined according to the guidelines of the therapeutics and assessment subcommittee of the American Academy of Neurology (AAN). These guidelines require two class I studies for level A evidence (effective or not effective). For level B evidence (probably effective/ineffective), one class I or two class II studies are required. Presence of only one class II study denotes level C (possibly effective/ineffective) evidence. Level U means efficacy is undetermined. Appendices 3.1 and 3.2 provide a summary of the AAN guidelines with descriptions of the study class and level of evidence (French and Gronseth 2008; Gronseth and French 2008). The Yale Medical Library's search system was used for literature search which encompasses a number of search programs including PubMed and Ovid.

Among the seven BoNT serotypes (A, B, C, D, E, F, and G), only types A and B have clinical utility. Three type A toxins (onabotulinumtoxinA, onaA; incobotulinumtoxinA, incoA; abobotulinumtoxinA, aboA) and one type B toxin (rimabotulinumtoxinB, rimaB) are approved by the FDA for use in the USA (Fig. 3.1). Table 3.2 illustrates the generic and trade names of these toxins, their manufacturer's name, and number of units/vial.

**Table 3.1** Pathophysiological mechanisms of neuropathic pain

| Level of the nervous system | Pathophysiological mechanisms |
|---|---|
| PNS | |
| Peripheral nerve | Release of pain-related mediators (BK, PG, TNFα, ILs, His, ATP, and potassium ions) |
| | Upregulation of TRP proteins in uninjured C fibers |
| | Dysregulation of the synthesis or the functioning of voltage-gated sodium channels |
| | Dysregulation of the synthesis or the functioning of potassium channels |
| Dorsal root ganglion | Increased activity in dorsal root ganglions |
| | Dorsal root ganglion infiltration by activated macrophages |
| | Increased synthesis of proinflammatory cytokines in dorsal root ganglions |
| CNS | |
| Spinal cord neurons | Functional reorganization (neuroplasticity) of dorsal horn nociceptive |
| Neurons | |
| | Increased release of glutamate and substance P |
| | Increased expression of Nav1.3 in dorsal horn second-order neurons |
| | Increased activity in voltage-gated calcium channels |
| | Selective apoptotic loss of GABA-releasing interneurons |
| | Reduction of KCC2 in lamina I neuron |
| | Intracellular changes induced by the activation of NMDA receptors or other receptors (i.e., glutamate metabotropic receptors) by excitatory amino acids released by primary afferents |
| | Microglial activation |
| Brain stem (descending pain-controlling systems) | |
| Loss of function in descending inhibitory opioidergic, serotonergic, and noradrenergic pathways | |
| Changes in the modulatory control of nociceptive pathways | |
| Brain | Functional reorganization (neuroplasticity) of thalamic and cortical (prefrontal and somatosensory) nociceptive neurons |

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*ATP* adenosine-5′-triphosphate, *BK* bradykinin, *CNS* central nervous system, *GABA* γ-aminobutyric acid, *His* histamine, *IL* interleukin, *KCC2* potassium chloride co-transporter 2, *Nav1.3* voltage-gated sodium channel 1.3, *NMDA* N-methyl-D-aspartate, *NP* neuropathic pain, *PG* prostaglandin, *PNS* peripheral nervous system, *TNFα* tumor necrosis factor-α, *TRP* transient potential receptor

## Technical Points

All toxins except incoA require refrigeration. With the exception of rimaA (which comes as an already prepared solution), all toxins need to be prepared with preservative-free saline. A dilution of 1–4 cc can be used in clinical practice. To prepare the solution, saline is drawn with a 20 or 21 gauge needle into a 2 or 4 cc syringe and then introduced into the vial. The vial is then gently shaken for a few seconds. In the case


**Fig. 3.1** FDA-approved botulinum neurotoxins (From Chen and Dashtipour 2013 © 2013 Wiley Publications, reprinted with permission from Wiley)

**Table 3.2** FDA-approved botulinum neurotoxins

| Name given by FDA | Trade name | Manufacturer | Vial (units) |
|---|---|---|---|
| OnabotulinumtoxinA (onaA) | Botox | Allergan Inc. | 100, 200 |
| IncobotulinumtoxinA (incoA) | Xeomin | Merz Pharm | 50, 100 |
| AbobotulinumtoxinA (aboA) | Dysport | Ipsen Pharm | 300, 500 |
| RimabotulinumtoxinB (rimaB) | Myobloc (US) | US WorldMeds | 2,500, 5,000, 10,000 |
| | Neurobloc (Europe) | | |

of incoA, it is recommended to invert the vial two to three times. The solution is then drawn with the same needle into a 1, 2, or 4 cc syringe. For injection, a 27.5 or 30 gauge needle is used. Depending on the depth of injection, the length of the needle may vary from 0.5 to 1.5 in.; for subcutaneous injection, a 0.5-in.-long needle suffices. Per manufacturer's recommendations, the prepared toxin should be used within 4–6 h.

Botulinum neurotoxins (BoNTs) are now used widely in clinical medicine for a variety of indications such as treatment of dystonias, spasticity, and migraine. In pain medicine, only chronic migraine is an approved FDA indication. All other areas are currently considered off label, although for several of them, the literature strongly suggests efficacy. The four aforementioned neurotoxins are generally considered safe in the recommended doses. Rare and serious side effects, however, have been reported. It is hence prudent before administering any BoNT, to obtain a signed acknowledgement from the patient about having reviewed the list of potential side effects.

## Postherpetic Neuralgia

Herpes zoster results from reactivation of varicella-zoster (VZ) virus usually in individuals who previously have had chicken pox and developed cell-mediated immunity after the infection. The reactivation takes place in cranial nerves or dorsal root ganglia with spread of the virus to sensory nerves and corresponding dermatome. Diabetic and immunocompromised patients are more prone to zoster infection.

The extent of pathology varies widely from patient to patient. There is often substantial reduction of epidermal nerve fibers (small unmyelinated fibers) and loss of subepidermal plexus. Reinnervation is slow and skin biopsy, even 10 years after the infection, shows incomplete innervation (Oaklander 2001). In one study, magnetic resonance imaging showed signal changes in the spinal cord and brain stem (56 %), and the cerebrospinal fluid demonstrated inflammatory cells in 61 % of the patients affected by acute zoster infection (Haanpaa et al. 1998). Varicella-zoster vaccination reduces development of PHN by 66.5 % between ages 60 and 80 (Oxman et al. 2005). Antiviral therapy reduces the risk of developing PHN (Wood et al. 1996). Concurrent steroid therapy does not reduce the risk of PHN but alleviates the initial acute pain (Whitley et al. 1996).

Pain associated with zoster infection may manifest before the rash (presymptomatic neuralgia), during the rash, or even later after the rash has cleared up. The typical PHN usually persists beyond 3 months after the zoster infection. The incidence of postherpetic neuralgia increases with age: 5 % for individuals younger than 60, 10 % between 60 and 69, and 20 % for age 80 or older (Yawn et al. 2007). Older age, severity of the initial acute pain (Thyregod et al. 2007), and presence of larger fiber neuropathy (A-beta fibers with loss of vibration) increase the risk of PHN (Baron et al. 1997).

### *Treatment*

PHN is one of the most severe forms of human pain. Affected individuals cope with poor quality of life and are often disabled by severe bouts of pain (Oster et al. 2005). A variety of oral and topical medications are currently in use for treatment of PHN. Gabapentin and pregabalin, due to their safer side effect profiles, are often used as first drugs sometimes in combination with tricyclic agents. More severe

forms of pain will require adding opioid agents, corticosteroids, or application of anesthetic patches. Cohen (2013) reviewed the subject of PHN and its treatment in a recent communication (Table 3.3). Most medications depicted in Table 3.3 are also used for treatment of other forms of neuropathic pain. Unfortunately, a large number of patients with PHN fail to respond to currently available medications.

## *BoNT Studies in Postherpetic Neuralgia*

Two double-blind studies have investigated the efficacy of botulinum toxin A in postherpetic neuralgia.

The first study by Xiao et al. (2010) assessed pain relief by visual analog scale (VAS) at 1, 7, and 90 days after subcutaneous injection of BoNT-A in 60 patients with PHN. Quality of life was measured by improvement in sleep hours. Patients were randomized and assigned blindly into three groups: BoNT-A, lidocaine, and placebo (20 in each group). The baseline level of pain and sleep disturbance was comparable between the three groups. The location of herpetic skin lesions was orofacial ($n=11$), cervical and upper extremity ($n=14$), thoracic ($n=18$), and lumbar and lower limbs ($n=17$).

A Chinese botulinum toxin A prepared by Lanzhou Institute was used for this study. The injecting solution was prepared by mixing 100 units of this toxin with 2 cc of preservative-free saline (5 units/cc). Injections were subcutaneous, grid-like, 1 cm apart, and into the region of tactile allodynia. Patients in the BoNT group had significantly better pain relief compared to the two groups on lidocaine and saline ($P<0.01$). BoNT analgesic response began at days 3–5, peaked at 1 week, and continued for 3 months. The improvement of sleep from BoNT was also superior to the lidocaine and placebo groups ($P<0.05$). Patients in the BoNT group also used significantly less opioids (22 % vs. 52 % and 66 %). Side effects consisted only of pain at the time of injection.

Apalla et al. (2013) conducted a prospective, double-blind, parallel study comparing the effect of BoNT-A (onaA) with placebo in 30 adult subjects with PHN. In the BoNT-A group, the toxin was diluted with 4 cc of normal saline and injected subcutaneously via a 30 gauge needle in a "chessboard manner." The dose per injection site was 5 units. A total of 100 units was used. The severity of pain was assessed by VAS (0–10) at baseline and then daily for the first 2 weeks, every 2 weeks until the 12th week, and every 4 weeks until the 24th week. The primary outcome was 50 % or more reduction in VAS score measured at week 4 compared to baseline. The secondary outcome was improvement of quality of sleep evaluated by a 5-point questionnaire (very bad to very good) recorded at the same time frames.

Maintenance of improved VAS scores beyond the first 4 weeks was also considered a secondary outcome. Significant VAS improvement was reported at 4 weeks and also over subsequent weeks (for the toxin group, $P<0.001$). Patients in BoNT also demonstrated significant improvement in quality of sleep and reduction of sleep scores along the same timelines.

**Table 3.3** Medications commonly used for treatment of acute pain associated with herpes zoster

| Medication | Dose | Dose adjustment | Maximum dose | Side effects |
|---|---|---|---|---|
| *Opioid and nonopioid analgesics* | | | | |
| Oxycodone | 5 mg every 4 h as needed | Increase by 5 mg four times daily every 2 days as tolerated | None specified, but should not exceed 120 mg daily except in consultation with a pain specialist | Drowsiness, dizziness, constipation, nausea, vomiting |
| Tramadol | 50 mg once or twice daily | Increase by 50–100 mg daily in divided doses every 2 days as tolerated | 400 mg daily; 300 mg daily if patient is >75 years of age | Drowsiness, dizziness, constipation, nausea, vomiting |
| *Glucocorticoids* | | | | |
| Prednisone | 60 mg daily for 7 days, then decrease to 30 mg daily for 7 days, then decrease to 15 mg daily for 7 days | None | 60 mg daily | Gastrointestinal distress, nausea, vomiting, mood changes, edema, glucose intolerance, increased blood pressure |
| *Anticonvulsants* | | | | |
| Gabapentin | 300 mg at bedtime or 100–300 mg three times daily | Increase by 100–300 mg three times daily every 2 days as tolerated | 3,600 mg daily | Drowsiness, dizziness, ataxia, peripheral edema |
| Pregabalin | 75 mg at bedtime or 75 mg twice daily | Increase by 75 mg twice daily every 3 days as tolerated | 600 mg daily | Drowsiness, dizziness, ataxia, peripheral edema |
| *Tricyclic antidepressants* | | | | |
| Nortriptyline | 25 mg at bedtime | Increase by 25 mg daily every 2–3 days as tolerated | 150 mg daily | Drowsiness, dry mouth, blurred vision, weight gain, urinary retention |
| *Topical therapy* | | | | |
| Lidocaine patch (5 %) | One patch, applied to intact skin only, for up to 12 h per day | None | One patch for up to 12 h per day | Local irritation; if systemic, absorption can cause drowsiness, dizziness |

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This table provides examples and is not meant to be comprehensive (Modified from Dworkin et al. by permission of Oxford University Press)

The controlled and blinded study of Ranoux et al. (2008) which demonstrated efficacy of onaA in neuropathic pain (rated class I by AAN subcommittee) also included four patients with PHN. The specifics of these four patients, however, were not provided. This study is discussed in detail in the section on post-traumatic neuralgia.

## *Case Report 3-1*

A 62-year-old female was referred to the Yale Botulinum Toxin Treatment Clinic for evaluation of severe right retroauricular pain. Patient specified the onset of pain to 2 years ago. At the onset, the pain involved both inside and behind the right ear. A course of antibiotics was not helpful. Few weeks later, with the appearance of typical skin lesions, zoster infection was diagnosed and treated with acyclovir. The skin lesions gradually improved, but the right retroauricular pain continued and grew in intensity. Some of the bouts of pain ended in severe headaches. The pain was described as jabbing and stabbing resulting in loss of sleep and marked apprehension in anticipation of the next bout. A variety of analgesic medications including gabapentin, pregabalin, and oxycodone were not helpful. The pain was often scored as 10 of 10 on visual analog scale and described as unbearable.

On examination, there was discoloration along with scars of zoster infection behind the right ear. A total of 60 units of onaA toxin was injected in a grid-like pattern behind the left ear subcutaneously at 20 points (3 units/point) using a 30 gauge needle (Video 3.1). The dilution was 100 units per 2 cc. Patient reported a sharp drop in pain frequency and intensity (VAS down from 10 to 3) 5 days after the injections. The pain then disappeared at week 2 postinjection and gradually reappeared at 2.5 months. Over the next 2 years, patient received similar treatments every 3 months. Each treatment resulted in significant reduction in pain. The last injection lasted 6 months with the returning pain reported as subtle (1 in VAS). Patient described no side effects. In an interview 2 years after treatment, the patient was very pleased with the outcome (Video 3.2).

## *Comment*

The author has treated six patients with PHN with subcutaneous injections of onaA. The dose ranged from 60 to 200 units based on the extent of the involved skin. The treatment was very effective in five patients (i.e., case 1). In one patient with extensive zoster infection of the chest, two treatments of onaA with similar doses failed to alleviate the pain.

Based on the above two class I studies, BoNT-A treatment possesses level A efficacy (effective) for treatment of PHN. The role of other BoNTs needs to be investigated. Failure of some patients with PHN to respond to onaA may be related to extensive pathology possibly extending to CNS.

## Post-traumatic Neuralgia

### *Pathophysiology*

Peripheral trauma triggers a cascade of events which involve nociceptor receptor sites, peripheral nerve endings, dorsal root ganglia (DRG), spinal cord neurons, and central sensory neurons. Damaged nerve endings often accumulate pain mediators (glutamate, substance P), and new sprouts demonstrate increased density of sodium channels (Katz and Seltzer 2009) which increases peripheral nociceptive firing and generates ectopic discharges. New sprouts show increased sensitivity to cytokines, prostaglandin, and catecholamines. This peripheral sensitization increases the volume of nociceptive volleys which enter the dorsal root ganglia and spinal cord.

Histologic changes which develop after peripheral trauma in DRG and spinal cord indicate increased neural excitation. In DRG, there is overgrowth of sympathetic nerves and abnormal linkage of A and C fibers (McLachlan et al. 1993). In the spinal cord, dark cells appear in dorsal horns which presumably represent dying inhibitory neurons of glycinergic and GABAergic types (Garrison et al. 1991; Todd and Sullivan 1990). Demise of inhibitory neurons leads to enhanced excitation of central neurons. It has also been shown that after peripheral injury, many large alpha/beta afferents (usually ending in Rexed area III) grow and penetrate more superficial levels (Rexed laminae II and I of dorsal horn) and gain access to low-threshold pain afferents (Yaksh and Caplan 1997).

### *Treatment*

Medical treatment consists mostly of administration of analgesic agents listed in Table 3.3. Additional treatments for persistent PTN include nerve block by single injection or infusion, transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (PNS), or spinal cord (dorsal horn) stimulation which leads to increased GABA release.

### *BoNT Treatment of Post-traumatic Neuralgia*

Ranoux et al. (2008) screened 61 consecutive patients of whom 29 met the criteria of neuropathic pain and eligibility for BoNT treatment. These patients were enrolled in a randomized, prospective, double-blind study which investigated the efficacy of onaA in neuropathic pain. Nineteen patients were women. Twenty-five patients had post-traumatic neuralgia and four patients had postherpetic neuralgia. In the post-traumatic group, 18 patients had surgical trauma and 7 nonsurgical trauma to single nerves. The primary outcome was self-reported level of pain in the past 24 h on an 11-point scale of brief pain inventory (0–10) from a diary. Pain level was assessed

at baseline and at 4 and 12 weeks. Secondary outcomes included degrees of brush allodynia, mechanical sensation and pain threshold, thermal sensations and pain threshold, as well as neuropathic pain symptom inventory; all were assessed at aforementioned timepoints.

A neurologist not involved in the study administered the BoNT-A (onaA) solution intradermally at points 1.5 cm apart. The dilution was 100 units in 4 cc of preservative-free saline. The mean number of injections was 20 + 8.3. The dose ranged from 20 to 190 units.

The pain intensity started to decrease from week 2 ($p = 0.02$) in favor of onaA and remained improved until week 14 ($p = 0.03$). The average pain intensity assessed at each visit improved in the toxin group (0.007). Allodynia to brush also improved significantly, and pain threshold to cold was decreased in the BoNT group. Injections were painful, but no patient reported any side effects.

## *Patient 3-2*

A 56-year-old woman was referred to the Yale Movement Disorder Clinic for evaluation of severe post-traumatic neuralgia, to be considered for BoNT treatment. Twelve years earlier, her car was forcefully rear ended after she braked hard in order to avoid hitting a car in front of her. The accident heavily bruised her right ankle and the lateral aspect of her right foot. The foot and ankle continued to ache, and an area of intense allodynia developed over the lateral malleolus extending up to the lower leg. A large number of medications failed to improve either the pain or the local allodynia. The most recent medications included Neurontin, pregabalin, tramadol, capsaicin ointment, and voltaren gel. In patient's words, "the physical, emotional, and psychological impact of my chronic pain defies description. Every night, I have to take Tylenol, Advil, Ambien and apply ankle soak, topical pain cream, and heat wrap in order to be able to sleep. With all this, many nights I am unable to sleep due to pain. Even the pressure of sheets would cause the pain to flare up. Sleeping on my side is impossible."

On examination, muscle strength was normal, but foot movements were slow and intensified the ankle pain. A large area of allodynia and hyperesthesia was present including the lateral aspect of the right foot extending 10 cm above the right ankle. The most intense allodynic region was over the lateral malleolus extending to 5 cm above (Fig. 3.2).

OnabotulinumtoxinA (onaA) was injected subcutaneously into the dorsolateral aspect of the right foot (50 units, 20 sites, grid pattern) including the region of lateral malleolus. Patient reported 30 % reduction of pain (7 on VAS) after the first injection and 90 % decrease after the second injection (VAS 1–2) 6 months later.

Patient noted, "the effect after the second injection was astounding. I stopped taking gabapentin and using pain wrap at night. I can now wear high-heel shoes and clothes that rub against my ankle. I am looking forward to wearing boots for the first time in 12 years!" (videotapes).

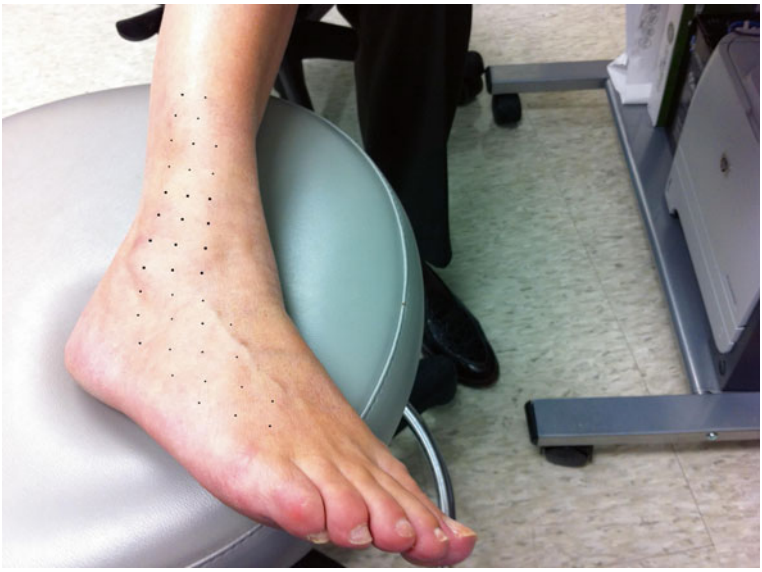

**Fig. 3.2** Region of right foot allodynia in patient 3-2. The most intense area is over and around the lateral malleolus shown by *larger* and *darker dots*

An examination 3 months after the second injection showed marked reduction of allodynia which was now much less intense and limited to a small area above the lateral malleolus.

### *Clinical Comment*

The level of evidence for efficacy of onaA for PTN is B (probably effective) based on one class I study. The case presented above is an example of PTN with severe allodynia showing a remarkable response to onaA after two treatments. A more significant response after the second or third injection with onaA has also been reported for chronic migraine (see Chap. 4). A number of patients with PTN may later develop complex regional pain syndrome (CRPS), a condition which is more difficult to treat. An important question is whether or not early treatment of PTN with onaA may prevent the development of CRPS in some patients.

## Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) often evolves from post-traumatic neuralgia. For reasons which are yet poorly understood, a traumatized limb affected by somatic pain gradually develops additional autonomic and trophic dysfunction. In

CRPS I, the causative factor does not damage or disrupt the nerve, whereas in CRPS II, the peripheral nerve is damaged. Causalgia, first described in detail by Weir Mitchell among soldiers with traumatized limbs during the American Civil War, belongs to the CRPS II category. Pain in CRPS has a burning and jabbing quality, and the involved limb has areas of allodynia and hyperesthesia. Autonomic dysfunctions can be in the form of coldness or warmth of the limb with hyper- or hypohydrosis. Trophic changes include skin atrophy, hair loss, and nail changes (Harden et al. 2013). Motor symptoms such as finger, hand, and arm dystonia and tremor may develop and cause further discomfort. Symptoms may progress proximally and result in pain and dystonia of the arm and shoulder muscles. In severe cases, loss of vascular supply threatens development of gangrene and may necessitate limb amputation.

## *Pathophysiology*

For years, primary dysfunction of the sympathetic system was held responsible for the development of CRPS. This view is now modified in favor of neuroinflammation and deranged autoimmunity with small C fiber damage playing a pivotal role. Damage to C fibers could lead to neurogenic inflammation, ectopic firing, vasodilation (via axon reflex), and/or hypoxic/ischemic injury (Weber et al. 2001; Coderre et al. 2004). Evidence exists that in some patients, neural inflammation extends to the spinal cord. In one patient with long-standing CRPS, tissue examination of the dorsal horn demonstrated significant activation of microglia and astrocytes with neuronal loss (Del Valle et al. 2009).

## *Conventional Treatment*

Treatment of CRPS is difficult and geared to relief of pain and modification of the course of the disease. Treatment of pain with tricyclic antidepressants, calcium channel blockers including gabapentin and pregabalin, serotonin/norepinephrine reuptake inhibitors, and locally delivered anesthetics is partially effective. Intranasal calcitonin (100–400 units) may relieve pain in some patients. In a blinded study, intravenous infusion of ketamine (NMDA antagonist) effectively reduced pain in 16 of 20 patients with follow-up of 6 months (Schwartzman et al. 2009). However, the recommended dose of 100 mg for 4 h/day for 10 days can be associated with significant hepatotoxicity requiring close liver function monitoring. Recently, a small double-blind crossover study of 12 patients suggested the efficacy of intravenous immunoglobulin (IVIG) (Goebel et al. 2010). In general, CRPS is considered a very difficult condition to treat.

### *BoNT Treatment of CRPS*

Argoff (2002) reported alleviation of pain, skin color, and local edema in 11 patients with CRPS following intramuscular injection of onaA. In agreement with this observation, a recent single case report described marked reduction of allodynia after subcutaneous injection of onaA in a patient with CRPS and dorsal hand allodynia (Birthi et al. 2012).

In contrast, in a blinded, controlled, parallel study, Safarpour et al. (2010) found no statistically significant difference between onaA and placebo in eight patients with severe CPRS allodynia. The authors also reported failure of onaA in an open trial of additional six CRPS patients. In another publication, however, these same authors (Safarpour and Jabbari 2010) reported significant improvement of proximal pain, proximal and distal dystonia, and shooting arm pain in two patients with CPRS after intramuscular injection of onaA into painful proximal muscles (deltoid, trapezius, levator scapulae, supraspinatus, upper thoracic paraspinal, and flexor digitorum superficialis) with a total dose of 300 units. In one of these patients, concurrent exquisite dorsal hand allodynia also gradually improved after 2 years of repeated proximal intramuscular injections. A recent retrospective report of 37 patients by Kharkar et al. (2011) also indicated improvement of CRPS after intramuscular injection of shoulder girdle muscles.

### *Clinical Comment*

The natural history of CPRS reflects a debilitating condition with poor prognosis. One long-term follow-up study found little improvement of symptoms with current methods of treatment (Schwartzman et al. 2009). The role of botulinum toxin treatment in CRPS is evolving, and at this point, the level of efficacy is U (undetermined) due to the lack of sizeable class I and II studies. The encouraging reports of open observations need to be examined by larger controlled studies. On the technical side, patients with severe allodynia (advanced CRPS) tolerate injections poorly. One important technical question is if combined subcutaneous and intramuscular injection would be more effective than subcutaneous or intradermal injection alone. Another equally important question is whether or not early and aggressive treatment with BoNTs would slow down the dismal course of CRPS.

## Metabolic and Drug-Induced Painful Peripheral Neuropathies

A large number of metabolic derangements and medications affect the peripheral nerves. In some, pain is a major symptom. Total coverage of all painful neuropathies is beyond the scope of this chapter. The focus of this section is on painful diabetic

neuropathy, the only metabolic neuropathy for which blinded, placebo-controlled clinical trial results with BoNT treatment are available. No blinded data on BoNT treatment of drug-induced peripheral neuropathies is available. Because of its importance and frequency, neuropathic pain related to chemotherapy is briefly discussed with a representative case presentation from the author's experience with onaA.

## *Diabetic Neuropathy*

Among metabolic disorders, diabetic neuropathy (DN) can be considered a model of metabolic neuropathic pain. Painful neuropathy is more common in type 2 diabetes with prevalence of 25–26 % (Boulton 2007) versus the 16 % reported for type 1 diabetes among the younger individuals (Barrett et al. 2007). The persistent pain often has a burning and aching quality. Examination shows reduced or lost sensory modalities consistent with DN but also areas of hyperesthesia and allodynia. Chronic pain causes anxiety and depression impairing the quality of life due to psychosocial distress and disrupted sleep.

### Pathophysiology

For many years, hyperglycemia was considered the reason for the development of pain in DPN. Recent data suggests hypoinsulinism and abnormal insulin signaling as more relevant factors (Romanovsky et al. 2006). At the molecular level, sodium channels, nonselective calcium channels linked to transient receptor potential receptor (TRP), and receptors for nerve growth factors (Trks) are all expressed highly in DRG neurons and believed to have a role in the pain of diabetic neuropathy. More recently, CaV3.2 T-type voltage-gated calcium channels (T-channels) have been identified as key players in the sensitized (hyperexcitable) state of nociceptive sensory neurons (nociceptors) in response to hyperglycemia and suggested as the basis for painful symptoms of diabetic neuropathy (Orestes et al. 2013).

### Treatment of Painful Diabetic Neuropathy (PDN)

The treatment strategy focuses on modifying the mechanisms which cause neuropathic pain (Table 3.1), the use of known drugs for neuropathic pain (Cohen 2013, Table 3.3), and control of hyperglycemia. Agents that increase hyperglycemia are to be avoided.

### BoNT Treatment in Diabetic Neuropathy

Two placebo-controlled, blinded studies have investigated the efficacy of onaA in painful diabetic neuropathy.

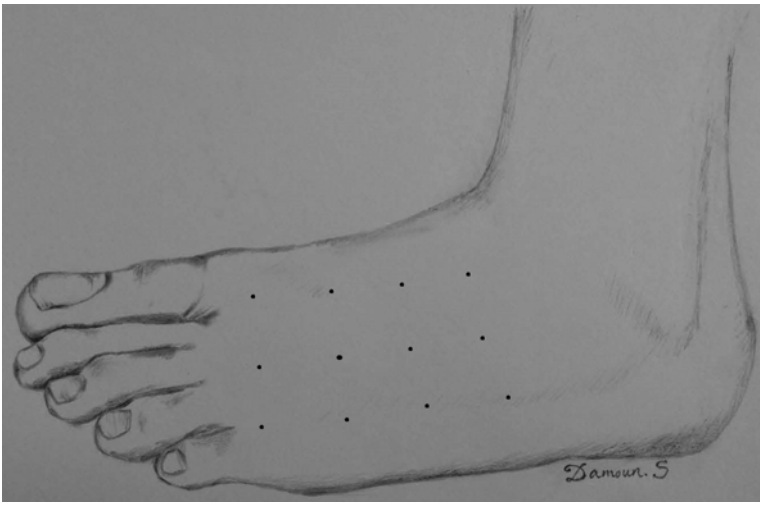


**Fig. 3.3** Grid pattern of intradermal injection advocated by Yuan et al. (2009) (neurology) for treatment of painful diabetic neuropathy (Created by Damoun Safarpour; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

Yuan et al. (2009) conducted a double-blind crossover study in 18 patients injecting onaA or saline intradermally in the hyperesthetic and allodynic foot regions (4 units/site in the case of onaA) (Fig. 3.3). The pain reduction measured by VAS was significant in favor of onaA at 1, 4, 8, and 12 weeks ($p < 0.05$). OnaA administration improved sleep at 1 week (using Chinese version of the Pittsburgh sleep quality index, CPSQI) ($P < 0.05$). Quality of life assessed by SF36 also improved in more patients in the onaA group (compared to placebo), but the difference was not statistically significant.

In another blinded, placebo-controlled crossover study, Chen et al. (2013) assessed the efficacy of onaA in 18 patients with painful diabetic neuropathy. Sensory perception was assessed by using von Frey filaments (tactile threshold TT) and mechanical pain threshold (using weighted syringes) of bilateral medial and lateral feet obtained at baseline and at weeks 1, 4, 8, and 12 after treatment. At weeks 1, 4, 8, and 12, both tactile perception and mechanical pain decreased markedly in onaA group compared to baseline.

## Comment

The studies cited above for allodynia of diabetic neuropathy are both class II. Two class II studies indicate a B level of evidence for efficacy (probably effective) for onaA in relieving the pain of DN. The efficacy of other type A toxins and type B toxin in DN deserves investigation. Other metabolic and drug-induced painful neuropathies also need to be studied.

## *Painful Neuropathy Related to Drugs and Chemotherapeutic Agents*

There are no controlled studies assessing the efficacy of BoNTs in drug-induced and chemotherapy-related painful neuropathies. The case below describes author's experience with one of the two patients in whom treatment with onaA resulted in marked improvement of pain associated with chemotherapy-induced allodynia.

### Patient 3-3

A 64-year-old man was referred to the Yale Botulinum Toxin Treatment Clinic for evaluation of severe burning pain of both feet. One year earlier, he had been diagnosed as having a myelodysplastic syndrome for which he had received stem cell transplant. The pain began a month after the transplant while he was receiving immune system-modifying agents (tacrolimus, CellCept, and prednisone). The pain first involved both upper and lower limbs equally but intensified in the feet over the succeeding months. He described the pain as frequent "electrical shocks" or "like a swarm of bees stinging you all at once." The most intense pain affected the dorsal and ventral aspects of the big toe and the adjacent dorsum of the foot bilaterally. The pain worsened at night and was described as "excruciating." Patient rated his pain in VAS as 10 out of 10. Treatment with a variety of analgesic medications including duloxetine, gabapentin, methadone, and oxycodone provided only minimal relief.

Neurological examination showed decreased light touch, pinprick, and vibration sense in the distal part of all extremities and absent ankle jerks. There was exquisite sensitivity to light touch in the dorsum and ventral aspects of the big toes and a small area on the dorsum of both feet close to the big toes which resulted in intense pain (severe allodynia) upon palpation. Each of these three areas, in each foot, was injected with 10 units of onaA subcutaneously. Six to eight sites were injected per area (1.5–2 units/site) for a total of 30 units per ft (Fig. 3.4). Within 2 weeks after this treatment, patient noted marked improvement. In evaluations performed at 4 and 8 weeks after treatment, patient reported his level of pain as 2 out of 10 "very low" in VAS. He expressed his level of satisfaction in PGIC (patient global impression of change) as "much improved."

### Comment

Painful neuropathy related to chemotherapeutic agents is a major issue in clinical oncology. If controlled trials can demonstrate efficacy of BoNTs in alleviating this form of neuropathic pain, it would be very beneficial to these patients who are often on polypharmacy and not enthused to take additional pain medications.

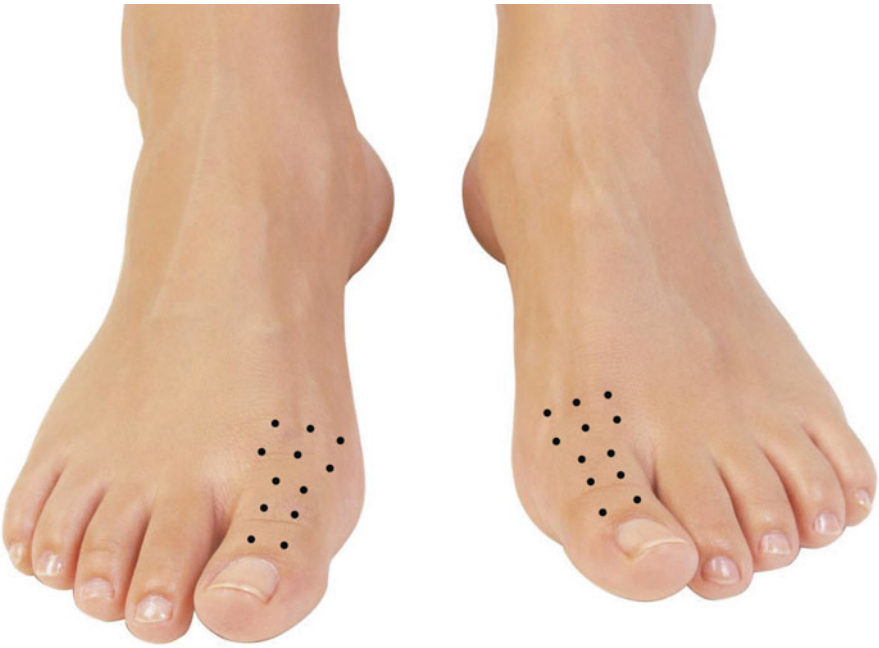

**Fig. 3.4** Patient 3-3. Areas of intense allodynia (injected by onaA) affecting the big toes and dorsum of the foot developed following treatment with immune-modifying agents for cancer

## Residual Limb Pain and Phantom Pain

With increasing frequency of military conflicts, pain associated with loss of limb has become a major medical management issue among soldiers. It is predicted that in the USA, the number of patients affected by this type of pain will exceed three million by the year 2050 (Zeigler-Graham et al. 2008). Pain associated with loss of limb can be a pain in the stump (residual limb pain, RLP) or felt in the region of the lost limb (phantom limb pain, PLP). The reported incidence of RLP after amputation is 22–43 % and for PLP is 66 % (Carlen et al. 1978; Jensen et al. 1983). The possible mechanism and pathophysiology of phantom pain is discussed in detail in a recent review (Hsu and Cohen 2013).

### *Pharmacological Treatment*

A Cochrane review of literature (Alviar et al. 2011) concluded that based on blinded studies, morphine, gabapentin, and ketamine demonstrate trends toward short-term analgesic efficacy in PLP, while memantine and amitriptyline were ineffective. No data on long-term efficacy is available. The role of calcitonin, anesthetics, and dextromethorphan requires further clarification. In clinical practice, gabapentin is now used increasingly

as the first drug of choice for treatment of PLP due to its safer side effect profile. Since long-term efficacy of drugs against PLP is low (less than 5 % in one large review, Sherman et al. 1984), exploration of novel therapeutic approaches is urgently needed.

### *BoNT Treatment of RLP and PLP*

Two clinical observations, each on a small number of patients, claimed BoNT administration into stump muscles improves phantom pain. In one study (Kern et al. 2004), four patients were injected with 2,500–5,000 units of rimabotulinumtoxinB into the arm and leg stumps (two patients each). Injections were performed at multiple trigger points. All patients reported improvement in stump pain, PLP attacks, and improvement of local allodynia. One patient noted significant improvement of sleep. Improvements lasted for "many weeks." In one patient, a 12-month follow-up showed almost total pain relief. In another study (Jin et al. 2009), the authors described significant improvement of phantom pain in three patients (two with accident injury and one with landmine injury) after EMG-guided administration of aboA (up to 500 units) into the stump muscles. All three patients reported level 3 (on a 0–3 scale) improvement on global clinical scale as well as substantial pain improvement on VAS. Pain improvement lasted 11 months. Patients were able to reduce their pain medications after BoNT treatment.

Unfortunately, these positive observations did not bear out in a recent prospective, parallel design, blinded study which compared the effect of onaA with that of combined lidocaine/methylprednisolone therapy (Wu et al. 2012). Investigators injected a total of 250–300 units of onaA or 10 mg Depo-Medrol in 1 % lidocaine in up to six tender points of 14 patients with RLP and PLP. There was no significant effect on phantom pain from any of the two agents. Both agents, however, significantly improved RLP and pain tolerance. OnaA's effect on RLP and pain tolerability was stronger than that of lidocaine/Depo-Medrol injection ($p=0.002$ vs. $p=0.06$ and $p=0.01$ vs. 0.07, respectively). The relief of RLP in both groups lasted for 6 months.

### *Comment*

Phantom pain is a fascinating area for BoNT research. Efficacy, if confirmed, would imply that peripheral administration of BoNTs can influence allodynia caused by central pain. The blinded study cited above and open observations suggest efficacy of onaA for RLP. At this time, the level of efficacy of BoNT is U (undetermined) for both RLP and PLP due to the lack of class I or II studies.

## Conclusion

Neuropathic pain is one of the most common forms of human pain. Failure of response to current analgesic medications is not uncommon. The data on type A toxin (mostly onaA) is encouraging and indicate efficacy or probable efficacy in

three major and common forms of neuropathic pain, namely, postherpetic neuralgia, post-traumatic neuralgia, and painful diabetic neuropathy. Controlled and placebo-controlled trials are necessary to assess efficacy of BoNTs in other painful metabolic and drug-induced neuropathies, complex regional pain syndrome, residual limb pain, and phantom pain. Much remains to be learned about the most effective technique of injection, most effective dose, optimum dilutions, and differences among BoNTs in the treatment of neuropathic pain.

## Appendix 3.1 AAN Classification of Evidence

| Class | Criteria | Level of evidence | Recommendation |
|---|---|---|---|
| I | Prospective, randomized, controlled, outcome masked, representative population with criteria A–E[a] | A: Two or more Class I studies | Established as effective, ineffective, or harmful |
| II | Prospective, matched cohort, representative population, masked outcome and meets A–E or RCT with one criteria in A–E lacking | B: At least one Class I or two Class II | Probably effective, ineffective, or harmful and recommended |
| III | Controlled trial, representative population, outcome independent of patient treatment | C: At least one Class II | Possibly effective, ineffective, or harmful, may be used at discretion of clinician |
| IV | Uncontrolled study, case series, case report, or expert opinion | U | Data inadequate or conflicting |

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[a]Criteria A–D: A = primary outcome(s) clearly defined, B = exclusion/inclusion criteria clearly defined, C = adequate accounting for drop-outs and cross-over with numbers sufficiently low to have minimal potential for bias, D = relevant baseline characteristics or appropriate statistical adjustment for differences, E = for non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs meet 3 cited criteria

## Appendix 3.2 AAN Classification of Recommendations

| |
|---|
| *A*- Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies)[a] |
| *B*- Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies) |
| *C*- Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies) |
| *U*- Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven |

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[a]In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if (1) all criteria are met, (2) the magnitude of effect is large (relative rate improved outcome 5 and the lower limit of the confidence interval is 2)

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