Chapter 5
Botulinum Neurotoxins and Chronic Low Back Pain

Abstract Chronic low back pain is a common condition with diverse etiologies. It is a major cause of functional impairment and disability. In recent years, our understanding of the pathophysiology of low back pain has improved significantly especially in regard to the contribution of dorsal root ganglia and pain mediators. The treatment of chronic low back pain is challenging. Most drugs have limited or short-term efficacy, and many produce undesirable side effects. In animal models, botulinum neurotoxins (BoNTs) have shown analgesic effects through different mechanisms. In human, onaA is effective in chronic migraine, and data suggests efficacy in other forms of neuropathic pain. Using the same dose and technique (multilevel injection into erector spinae), one class II (double blind, placebo controlled) and one prospective, 16-month, open-label study have provided evidence of possible efficacy (level C) in chronic low back pain. Future studies should focus on etiologically distinct subgroups of patients with chronic LBP and take advantage of using the dose and techniques that have already shown promising results.

Keywords Botulinum toxin • Botulinum neurotoxin • Low back pain • Chronic low back pain • OnabotulinumtoxinA • AbobotulinumtoxinA

Introduction

The annual incidence of clinically significant low back pain (pain level of 4 or more on a 10-point scale) with functional impairment is approximately 10–15 % (Carragee et al. 2004). Epidemiological studies indicate that 75–80 % of all people suffer from low back pain some time during their lifetime (Andersson 1999).

Chronic low back pain (cLBP) is defined as pain in the low back lasting beyond 6 months. Approximately 8–10 % of all low back pains evolve into chronic pain. Chronic low back pain is a major cause of disability and early retirement. In the UK, it accounts for 13 % of absenteeism from work (Speed 2004) and imposes an annual burden of 6.65 billion pounds on the economy (Maniakadis and Gray 2000). In the

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USA, almost a quarter of century ago, the economic burden was estimated to be $50–100 billion dollars/annum (Fromyer and Cats-Baril 1991). Among German athletes, Schmidt et al. (2014) have reported a 1-year prevalence of 57 % and a lifetime prevalence of 66 % with the highest lifetime prevalence of 77 % noted among volleyball players.

Human low back is associated with a complex anatomy and physiology. All major anatomic elements of lumbosacral area (skin, muscles, bones, discs, dura, ligaments) have rich innervation and, when disturbed, are capable of producing low back pain. Direct involvement of neural elements (nerve roots) by compression or inflammation can also cause cLBP.

Botulinum neurotoxins have an analgesic effect and are reported to alleviate pain in a number of human pain conditions (Jabbari and Machado 2011). Since BoNTs are introduced through a muscular route and muscles of low back are major contributors to low back pain, the anatomy of low back muscles is reviewed here in some detail.

Anatomy of Low Back Muscles

The lumbosacral area contains a number of muscles arranged at different levels. These muscles stabilize the spine and allow movement of the low back in different directions (flexion, extension, rotation).

Erector spinae (ES) are the most superficial of the low back muscles. At lumbar region, the ES consists of a single muscle mass with three distinct groups: medially located spinalis, laterally located iliocostalis, and longissimus which is between these two (Fig. 5.1). The lower fibers of these muscles attach to the sacrum and iliac crest. Rostrally, the three muscles separate from each other approximately at L1–T12 vertebral level. The fibers of iliocostalis attach to T7–T12 ribs. The fibers of lumbar spinalis and longissimus attach rostrally to the transverse and spinal processes of lumbar and thoracic vertebrae. Unilaterally, ES provides lateral flexion and rotation to the opposite side. Bilaterally, these muscles extend the spine. The nerves for erector spinae originate from dorsal division of the spinal nerves.

Quadratus lumborum (QL) and multifidus muscles are located deeper than ES muscles (Fig. 5.1). QL is often implicated in low back pain. QL is rostrally attached to the lower level of the 12th rib and the transverse processes of the first four lumbar vertebrae. Its fibers end distally via aponeurosis to the lumboinguinal ligaments and attach to the medial part of iliac crest. Unilateral contraction of OL produces ipsilateral flexion of lumbar spine, whereas bilateral contraction helps with extension of the spinal column. Quadratus lumborum is innervated by the ventral rami of the 12th thoracic and upper three or four lumbar spinal nerves. Blood supply is derived from the lumbar arteries, lumbar branches of iliolumbar artery, and branches of subcostal artery.

Multifidus muscle fills up the groove in either side of the spinal processes of the vertebrae from the sacrum to the coccyx. The multifidus is composed of thin fasciculi which arise from the sacrum (as low as the fourth vertebrae), aponeurosis of the origin of sacrospinalis muscle, posterior medial surface of the ilium, and posterior

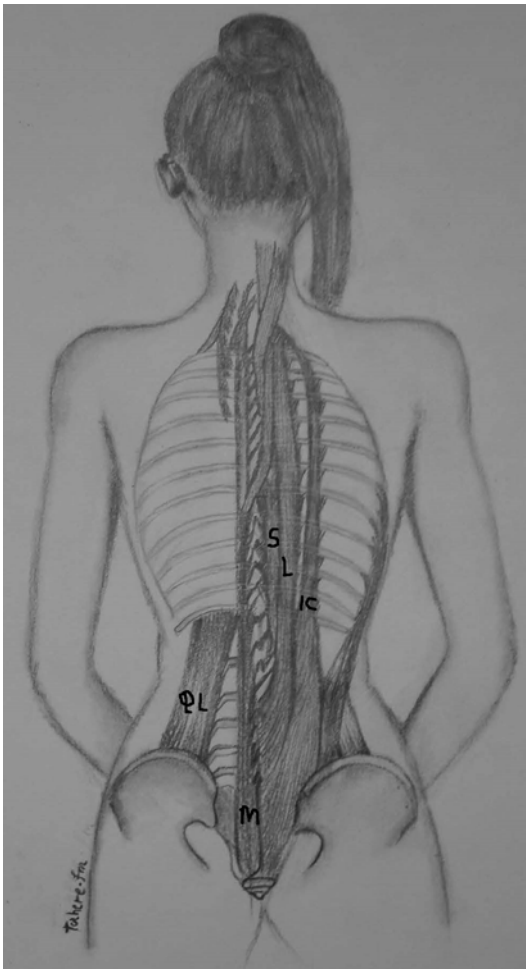

Fig. 5.1 The major muscles of low back: superficial layer (ES shown on the *right*,) and deep layer (quadratus lumborum marked *QL* and multifidus marked *M* and shown on the *left*). Spinalis (medial marked *S*), longissimus (*middle* marked *L*), and iliocostalis (lateral marked *IC*) join at T12–L1 level and make a single mass of erector spinae at the lumbar region (Created by Tahereh Mousavi; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

sacroiliac ligament. In the lumbar region, its fibers attach to mamillary processes of all lumbar vertebrae. Deeper fibers connect to L2–L4 lumbar vertebrae and work to stabilize the joints at each segmental level. At the lower lumbosacral region, more superficial multifidus fibers are close to the skin due to the thinness of the overlying ES in this region. Multifidus muscles, like facet joints, are innervated by the medial branch of the dorsal ramus of the spinal nerves.

Pathophysiology of Chronic Low Back Pain

Muscle strain and disturbance play a major role in the pathophysiology of mechanical low back pain. Major low back muscles such as ES and QL are richly innervated. Irritation of nerve endings may lead to accumulation of pain mediators (glutamate,

calcitonin gene-related peptide, and substance P) at the periphery causing peripheral sensitization. In patients with anatomically tight compartment for ES muscles, the compressed muscle can cause pain and discomfort especially during exercise, the lumbar compartment syndrome (Nathan et al. 2012).

Recently, the role of dorsal root ganglia (DRG) in chronic disc disease leading to low back pain has attracted much attention. It has been shown that DRG is very sensitive to pressure, and even light compression can cause long periods of repetitive firing (5–25 min) in DRG neurons (Howe et al. 1977). The ruptured disc material, due to proximity to DRG, can influence DRG neurons and upregulate expression of pain mediators and inflammatory agents to produce or enhance pain. In rats, experimental disc puncture at L5–L6 level causes persistent upregulation of calcitonin gene-related peptide (CGRP) in lumbar DRG neurons for the entire 8-week course of the study and a transient (2 weeks) increase in expression of inflammatory agents (interleukin-6, nerve growth and tumor necrotizing factors) in DRG (Miyagi et al. 2011). In a similar disc injury experiment in rats, after injury, there is upregulation of tetrodotoxin-sensitive sodium channel (NaV1.7), in L1–L5 DRG neurons. NaV 1.7 channels are associated with sensory transmission in sensory nerves (Sadamasu et al. 2014). Disc injury related to injection of Freund adjuvant into L5 disc results in increased expression of CGRP, substance P, and nerve growth factor both in DRG and the thalamus lasting for 8 weeks (Jung et al. 2011). A sizeable number of DRG neurons that innervate vertebral bodies are also CGRP positive (33 % of those innervating L5 vertebra) which suggests a role for this arrangement in bone-generated low back pain (Ohtori et al. 2007).

Facet joint disease is another condition often associated with chronic low back pain. Wakai et al. (2010) have shown that many DRG neurons have dichotomized axons which project both to facet joints and to low back muscles. These could be the source of referred pain. Approximately 17 % of all DRG neurons innervating the facet joints have other axons that extend to the lower back muscle.

The role of sympathetic nervous system in maintaining pain and its chronicity has long been suspected based on anatomical studies showing massive sprouting of sympathetic fibers into DRG after peripheral injury (McLachlan et al. 1993). Normally no sympathetic fibers are inside DRG, and noradrenergic innervation is present only in the adjacent blood vessels. Following peripheral injury, inflammation develops in DRG and sympathetic ganglia with influx of macrophages and T cell lymphocytes into DRG. This leads to the release of cytokines and increases discharge of DRG neurons. Sympathectomy or removal of sympathetic ganglia decreases the influx of macrophages and T cells into DRG and, consequently, decreases the magnitude of inflammation (McLachlan and Hu 2014). Sympathectomy attenuates the excitability of dorsal root ganglion neurons and pain behavior in a lumbar radiculopathy model (Iwase et al 2012). In chronic low back pain caused by root or DRG injury, sympathetic nervous system hyperexcitability may play a role in the maintenance of pain (sympathetically maintained pain).

In chronic pain states, peripheral sensitization (PS) due to accumulation of pain mediators and inflammatory agents leads to central sensitization (CS) that is believed to contribute to pain chronicity. This CS occurs at multiple levels of CNS

starting with the spinal cord neurons and followed by the brain stem, thalamic, and cortical levels. There is evidence from molecular biology, electrophysiological investigations, and neuroimaging studies that pathological conditions associated with chronic low back pain are capable of inducing central sensitization. In conditions such as herniated disc or trauma, DRG and spinal nerve injuries lead to the generation of ectopic discharges in DRG neurons causing hyperexcitability of spinal cord sensory neurons. Light compression of DRG by experimentally induced nucleus pulposus increases evoked responses in the posterior thalamic neurons for a minimum of 40 min (Nilsson et al. 2013). Functional MRI of patients with chronic low back pain compared to asymptomatic age-matched volunteers has shown augmented activation in premotor, supplementary motor, insula, and anterior cingulate cortex in patients with cLBP (Kobayashi et al. 2009).

Medical Treatment of Chronic Low Back Pain

In clinical practice, a large number of analgesic agents are used for the treatment of chronic low back pain; these include non-anti-inflammatory analgesics (aspirin, acetaminophen), nonsteroidal anti-inflammatory agents (NSAID), tricyclic and tetracyclic antidepressants, muscle relaxants, cyclooxygenase-2 inhibitors, antispasticity agents (tizanidine), anticonvulsants (gabapentin, pregabalin), serotonin/norepinephrine inhibitors (duloxetine), opioid-like agents (tramadol), strong opioids (oxycodone, OxyContin), and topical anesthetic agents. Tricyclic antidepressants cause a 20–40 % reduction over placebo in short follow-up (4–8) weeks, but their long-term effect is not known (Staiger et al. 2003). The anticholinergic side effects are also of concern in older patients. Prospective and control studies with some other agents (non-NSAID analgesics, NSAID, muscle relaxants, and cyclooxygenase inhibitors) have shown either no or marginal improvement over placebo in chronic low back pain (Van Tulder et al. 2000, 2003; Nussmeier et al. 2005; Coats et al. 2004; Ostelo et al. 2005; Solomon et al. 2005). In a 12-week study (Vorsanger et al. 2008), both 200 mg and 300 mg of tramadol moderately improved low back pain compared to placebo ($p = 0.052$ and $p = 0.009$); the disability index, sleep quality, and patient assessment score also improved as secondary measures ($p = 0.012$). Topical NSAID diclofenac has shown some promise in reducing osteoarthritic pain, but systematic studies in chronic low back pain are lacking. In acute and subacute low back pain, one prospective, open-label study has suggested efficacy of lidocaine patch to improve pain and quality of life, and these positive effects were associated with high score in patient satisfaction (Gimbel et al. 2005). Controlled studies in chronic low back pain with lidocaine patch are not available. The most recent Cochrane review of literature on the effect of opioids on pain and function of patients with low back pain encompassed 15 blinded studies and 5,600 patients during the period of 2007–2012 (Chaparro et al. 2014). Both tramadol (weak opioid function) and strong opioids improved chronic low back pain and function over placebo (moderate for pain, mild for function). Two studies found a comparable

effect in chronic low back pain for opioids with tricyclic antidepressants. No significant side effects were noted. None of the studies addressed long-term efficacy and safety. The long-term use of opioids is confounded by the development of addictive behavior.

In a recent review of chronic low back pain, Uhl et al. (2014) recommended tricyclic antidepressants (nortriptyline 25–150 mg daily), tramadol ER (100–300 mg daily), and lidocaine patch (5 %, one to three patches topically up to 12 h) as the first line of medical treatment. In view of limited supportive literature, the long-term efficacy of tramadol ER and lidocaine patch in treatment of cLBP is not well established. Despite medical therapy, most patients with chronic low back pain continue to experience pain and are not satisfied with their level of pain management.

Physical therapy (PT) is aimed to reduce pain, and therapists can educate patients to perform passive and active movements which potentially may prevent progression of low back pain and disability. While PT is commonly used in management of cLBP, well-designed studies are scant and methodological problems and paucity of high-quality investigations prevent drawing conclusions regarding the precise efficacy of physical therapy (Calvo-Muñoz et al. 2013).

Massage and heat and cold applications are temporarily effective for pain but show no long-term benefits. The few available high-quality studies advocate that spinal manipulative therapy (SMT) has no advantage in management of chronic low back pain (Rubinstein 2011). A recent review of yoga in chronic low back pain (ten randomized trials) suggested strong evidence for short-term and long-term effect on pain and moderate effect on pain-related disability (Cramer et al. 2013).

Transcutaneous electrical nerve stimulation (TENS) has been found to be ineffective based on two negative class I studies (level A evidence, AAN criteria—Appendices 3.1 and 3.2) (Dubinsky and Miyasaki 2010). Acupuncture data in low back pain are hard to interpret due to heterogeneity of participants and suboptimal quality of most studies. Improvements in pain and function are reported in some controlled studies, but the effects are transient (Rubinstien et al. 2010). Studies of ultrasound and shock therapy are limited, and available evidence suggests no appreciable effect on pain or functionality (Seco et al. 2011). Epidural injections with anesthetic agents (with or without steroids) improve pain flairs in cLBP, but the effects are generally transient. A recent review of the literature on this subject found 15 blinded, placebo-controlled studies with best results reported for radiculopathies due to disc herniation and spinal stenosis (Parr et al. 2012).

Surgical treatment of low back pain has produced mixed results. Spinal fusion alleviates pain and improves function in patients with degenerative spine disease, but the positive effects may not last long. Minimal spinal surgery without open surgery (with interbody fusion) in selected patients has produced good short-term results. Longer observations are needed, however (Spoor and Öner 2013).

A Cochrane review of six high-quality publications provided strong evidence that behavioral therapy had a moderate effect in decreasing pain, but no noticeable effect on patients' functional status or behavioral health. The review concluded that both the type of patients that benefit from behavioral therapy and the type of behavioral therapy which is most effective still need to be determined (Van Tulder et al. 2001).

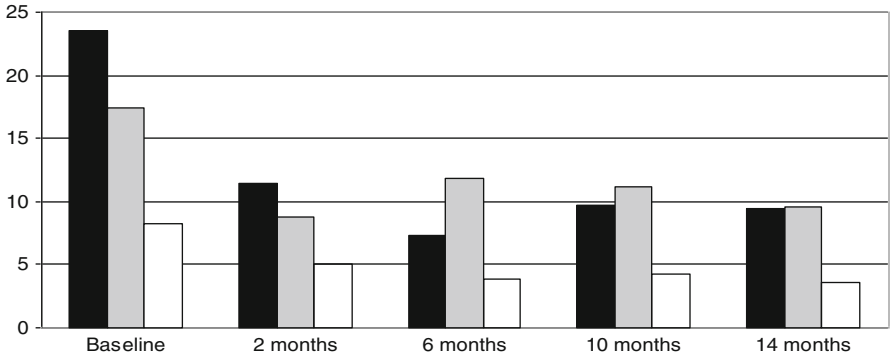

Fig. 5.2 Open-label study of onaA in cLBP with 14 months follow-up: *OLBPQ* Oswestry Low Back Pain Questionnaire (range 0–50), *PIQ* Pain Impact Questionnaire, *VAS* visual analog scale (range 0–10 cm). Compare to baseline *P* values for all three measures (<0.05). Mean pain days (PIQ), *dark*; OLBPQ, *gray*; and VAS, *white*, values before treatment and at 2 months after each treatment (injections are given at baseline and for most patients at 4, 8, and 12 months). Pain days and VAS are assessed over the preceding 28 days (Jabbari et al. 2006. © 2006, John Wiley and Sons)

Evidence for Efficacy of BoNTs in Chronic Low Back Pain

Two studies published from the Walter Reed Army Medical Center (WRAMC) first addressed the issue of BoNT efficacy, tolerability, safety, and quality of life in chronic LBP. The first study was double blind and placebo controlled (Foster et al. 2001). The second one was open label and prospectively assessed multiple treatment results (every 4 months) over a period of 14 months (Jabbari et al. 2006). Both studies used a similar protocol in respect to technique, dosing, and rating scales. The technique was based on the hypothesis that treatment results may not be optimal unless the whole length of erector spinae (ES) muscles in the lumbar region is exposed to and influenced by BoNT therapy. Hence, regardless of the location of pain or tender/trigger points (if present), injections were performed at five lumbar paraspinal levels (into lumbar ES) with a total dose of 200 units for unilateral LBP (blinded study) and 400–500 units for bilateral LBP (open study) (Fig. 5.2). Both studies used onabotulinumtoxinA (onaA). The third study performed by a different group reported on efficacy of aboA in a group of patients with chronic low back pain due to myofascial pain syndrome.

Study 1 (Foster et al. 2001)

Class II (using AAN criteria, Appendices 3.1 and 3.2). In this first blinded and placebo-controlled study of a BoNT in chronic low back pain, investigators randomized 31 subjects, 15 into the BoNT group and 16 into the placebo group. The inclusion criteria consisted of LBP of more than 6 months duration, unilateral or predominately unilateral LBP (level of 4 or more at visual analog scale (VAS)),

failure to respond to at least two major medications, and patients of 18 years or older. The exclusion criteria consisted of known hypersensitivity to onaA; pregnancy or planned pregnancy; presence of neuromuscular junction disorders; being on medications known to cause neuromuscular junction dysfunction; MRI evidence of severe disc disease, canal stenosis, or acute lesions of lumbosacral area requiring urgent medical or surgical intervention; and anesthetic or corticosteroid injections to the lumbosacral spine within 12 weeks of enrollment. Patients who were involved in litigation, seeking significant disability for low back pain, or with evidence of secondary gain were also excluded. The mean age of the study group was 46.4 years for onaA group and 47 years for the control group (range 20–73). The mean duration of pain was 8.1 years for the BoNT-A group and 5.7 years for the control group (range 6 months to 30 years). Patients were instructed to continue their analgesic medications during the study but not to change the dose, while avoiding new analgesics altogether. They were also instructed to make no changes in their physical therapy regimen as prescribed by routine clinical practice.

In the BoNT group, each patient received a total of 200 units of onabotulinumtoxinA (onaA) into the erector spinae (ES) on the side of unilateral or predominately unilateral pain. The ES muscle was injected at 5 points, L1, L2, L3, L4, and L5 levels, 40 units per level regardless of pain location. The dilution used was 100 units/cc. The baseline level of pain and degree of disability were documented by using the visual analog scale (VAS) and the Oswestry Low Back Pain Questionnaire (OLBPQ). Evaluations were performed at baseline, 3 and 8 weeks using VAS, and at baseline and 8 weeks with OLBPQ. The primary outcome measure was 50 % or more reduction in pain as defined by VAS at 8 weeks.

At 3 weeks, 11 of 15 subjects who received onaA (73.3 %) had >50 % pain relief versus 4 of 16 (25 %) in the control group ($p=0.012$). At 8 weeks, 9 of 15 (60 %) subjects in the onaA group and 2 of 16 (12.5 %) in the control group expressed relief ($p=0.009$). A repeat OLBPQ at 8 weeks showed significant improvement of quality of life in 10 of 15 (66.7 %) in the BoNT group versus 3 of 16 (18.8 %) in the control group ($p=0.011$). None of the patients experienced any side effects. It was concluded that paraspinal administration of onabotulinumtoxinA at five lumbar levels into ES is safe and can relieve pain and improve the quality of life in patients with predominantly unilateral chronic low back pain.

Study 2 (Jabbari et al. 2006)

Prospective, open label with repeated injections, 14 months. In this prospective study, the effect of BoNT-A on chronic LBP was investigated over a period of 16 months. The cohort consisted of 75 patients with chronic LBP refractory to medical or surgical treatment. The inclusion and exclusion criteria were the same as those of Study 1 with the exception of including patients with bilateral low back pain. The dose and technique were also similar to Study 1, with a minor modification (an extra dose of 10–20 units was administered more laterally into the bulk of

the erector muscles at the level of most discomfort). The patients had a mean age of 46.1 years (range 21–79) and mean pain duration of 9.2 years (range 7 months to 50 years). Of the 75 patients, 21 were female and 84 % of the entire cohort had bilateral pain. Other factors noted among the cohort included previous back surgery (n:14), root pain (n:20), epidural steroid injections (n:19), and narcotic analgesic use (n:36). Magnetic resonance imaging (MRI) showed a variety of low back pathology (50 %), but none were severe or acute. The most common pathologies consisted of chronic degeneration of the spine, canal stenosis, and chronic disc protrusions. Patients were instructed not to change their analgesic medications and continue with their physical therapy during the course of the study. Pain intensity (VAS), pain frequency (pain days measured in the Pain Impact Questionnaire (PIQ), Oswestry Low Back Pain Questionnaire (OLBPQ)), and patient level of satisfaction were assessed at baseline, 3 weeks, and at 2, 4, 6, 8, 10, 12, and 14 months. OnaA was injected into the paraspinal muscles at four to five levels (between L1 and S1) unilaterally or bilaterally depending on individual patient's pattern of pain. The dose per site was 40 units with exceptional patients receiving an additional 40–50 units at one level (more laterally) if the local area of pain extended laterally. The total dose per session ranged from 200 to 500 units. Re-injections were performed at 4 months if pain returned. Most patients had re-injections every 4 months. At 3 weeks, 40 patients (53 %) and, at 2 months, 39 patients (52 %) reported significant pain relief. The change in mean VAS, mean OLBPQ, and PIQ was significant compared to the baseline at 2 months after each injection period ($p<0.005$) compared to baseline and remained so over subsequent treatments. Among initial responders, 91 % continued to respond over the length of the study (Figs. 5.1 and 5.3). Nine of 20 patients (45 %) with root pain reported diminished root pain after treatment. After the first treatment, three patients (4 %) had mild flu-like symptoms which lasted 2–5 days. No other side effects were noted.

Study 3 (De Andres et al. 2010)

The authors enrolled a total of 28 patients (20 females) with chronic myofascial pain in the low back region. All patients had distinct trigger points which upon pressure evoked intense referred pain. The involved muscle distribution was as follows: psoas (18.5 %), quadratus lumborum (18.5 %), and psoas plus quadratus lumborum (63 %). The study was designed to evaluate prospectively and blindly the efficacy of onabotulinumtoxinA versus saline or bupivacaine. Twenty-seven patients completed the study. All patient received unilateral onaA injections into quadratus lumborum and iliopsoas (IS) muscles. On the contralateral side, 13 patients received bupivacaine (0.25 %), and 14 subjects received NaCl (0.9 %). The injected onaA solution was 100 units/cc. Each muscle (QL or IS) received 50 units fluoroscopically, injected deep into the muscle at one site.

Inclusion criteria were as follows: mechanical low back pain longer than 6 months duration; age 20–70; existence of bilateral trigger points with associated referred

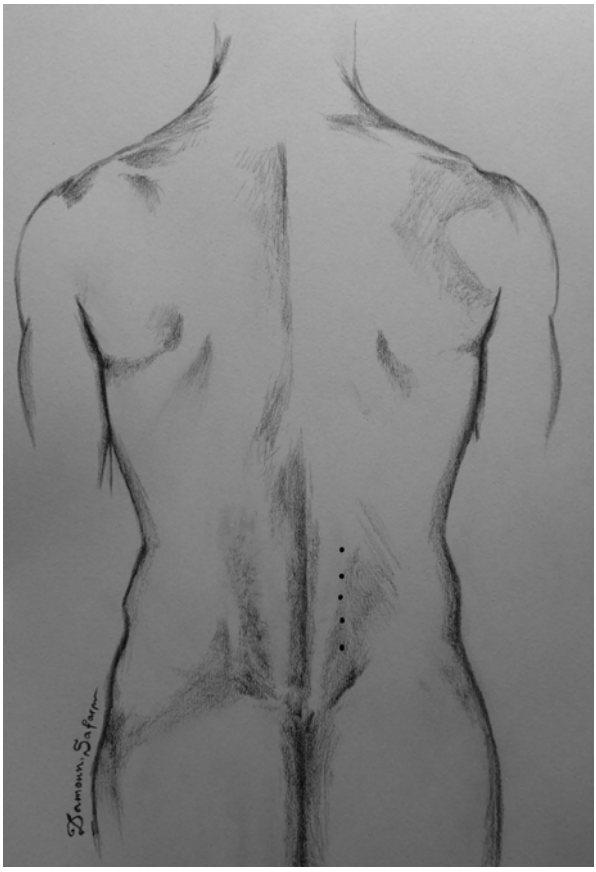

Fig. 5.3 Recommended locations of BoNT injection for chronic low back pain (Created by Damoun Safarpour; published with kind permission from © Bahman Jabbari 2014. All Rights Reserved)

pain in the iliopsoas muscle, quadratus lumborum muscle, or both; and no response to conservative medical and physical therapy. Patients with previous back surgery, spondylolisthesis, facet joints arthropathy, known or suspected hypersensitivity to BoNTs, neurologic deficits in the painful area, neuromuscular junction or motor neuron diseases, diagnosis of fibromyalgia, and inflammation or infection of the injection sites were excluded.

The primary outcome was the difference between VAS score on the side of BoNT injection and the side of saline or bupivacaine injection at 15, 30, and 90 days. Authors used five different questionnaires to evaluate the effects of treatment on daily life activities and psychological status of the patients (Hospital Anxiety and Depression scale [HAD-A and HAD-D], Lattinen, Oswestry, and Spielberger State-Trait Anxiety Index).

OnaA administration did not significantly reduce VAS scores compared with contralateral NaCl or bupivacaine injections. Nonetheless, a trend toward significance was seen only in the BoNT group in respect to VAS score. The authors, however, concluded that administration of onaA provided the subjects with significant pain relief but cautioned against its cost.

Table 5.1 Yale Study: Assessment of efficacy of abobotulinumtoxinA in chronic low back pain

	Week 0 Visit 1	Week 4 Telephone	Week 6 Visit 2	Week 8 Telephone	Week 10 Telephone	Week 12 Visit 3	Week 14 Telephone	Week 16 Visit 4
Eligibility, consent	X							
History/ physical	X		X			X		X
VAS	X	X	X	X	X	X	X	X
ACPA's QoL scale	X		X			X		X
SF-36	X		X			X		X
PGIC		X	X	X	X	X	X	X
Oswestry scale	X		X			X		X
Side effects		X	X	X	X	X	X	X
Injection	X							

VAS visual analog scale, *ACPA's QoL scale* American Chronic Pain Association's Quality of Life Scale, *SF-36* Short Form-36 quality of life questionnaire, *Oswestry scale* oswestry low back pain disability questionnaire, *PGIC* patient global impression of change

Yale Ongoing BoNT/Low Back Pain Protocol

There is an ongoing, investigator-initiated, single-center protocol at Yale to assess the efficacy and safety of abobotulinumtoxinA (aboA) in patients with chronic low back pain, funded by Ipsen Pharmaceuticals. A total of 90 subjects will be enrolled allowing for 12 % dropout. The inclusion criteria consist of age over 18 years, uni- or bilateral low back pain of more than 6 months duration, failure to respond to pain medications, and a pain level of >4 in VAS. Exclusion criteria are as shown in Ipsen brochure and similar to those of the aforementioned WRAMC studies. Subjects with a history of prior back surgery are excluded. aboA is injected into erector spinae muscles unilaterally or bilaterally (depending on their pain pattern). The total dose per site is 500 units (approximately equal to 200 units of onaA). Each lumbar ES is injected at levels L1, L2, L3, L4, and L5 and with100 units of aboA per level. Table 5.1 shows rating scales and frequency of evaluations in this study. The primary outcome of the study is the proportion of patients with VAS <4 in aboA group compared to placebo at week 6. So far, 33 patients have been enrolled, and 22 patients have completed the study. Table 5.1 shows the design of the ongoing Yale study for assessment of efficacy and safety of abobotulinumtoxinA in chronic low back pain.

Patient 5-1

A 57-year-old Caucasian male suffered from chronic low back pain for 10 years. The pain began insidiously, gradually increased in intensity, and became daily over the past 2 years. The pain concentrated in the lower lumbar region. He described no

radicular pain. Episodes of severe exacerbations were frequent and disabling. Severe episodes were rated as 10 out of 10 on VAS scale. He used a large number of analgesic medications over several years with no relief. His last pain medication was gabapentin (800 mg three times daily) and Cymbalta (90 mg daily). The patient was taking oxcarbazepine (600 mg twice daily) and lamotrigine (200 mg twice daily for depression). Lumbosacral magnetic resonance imaging disclosed no significant abnormality and only mild degenerative changes. Neurological examination including assessment of cognition, cranial nerve, motor, sensory, and cerebellar functions, speech, and gait was normal.

AbobotulinumtoxinA (aboA), 500 units on each side (100 units per each lumbar level), was injected into the erector spinae muscles under EMG guidance (Video 5.1). Patient was evaluated monthly with VAS and patient global impression of change for 4 months. Two weeks after the initial treatment, he reported absence of low back pain. VAS scores at months 1, 2, 3, and 4 were at 0, 1, 1, and 2 levels, respectively. At 4 months, he reported his experience with aboA treatment as very satisfactory (Video 5.2, patient interview). There were no side effects.

How Does the Administration of Botulinum Toxin Improve Low Back Pain?

The exact mode of action of botulinum toxin A in chronic low back pain still remains to be determined. Based on animal and human research data, several plausible mechanisms exist:

1. In muscles, both A and B toxins produce relaxation via inhibiting the release of acetylcholine in the neuromuscular junction. This could explain some of the pain relief especially when low back pain is associated with muscle spasms. Furthermore, decreased muscle tone is often associated with a reduction in muscle bulk as well documented when BoNTs are used in hyperactive movement disorders. This decrease in muscle bulk (especially in the ES muscle) may be helpful when back pain is attributed to anatomically tight compartment (lumbar compartment syndrome Nathan et al. 2012).
2. As described under pathophysiology of cLBP, many causative factors, especially protruded disc, produce marked accumulation of pain mediators (CGRP, substance P) and inflammatory agents (cytokines) in DRG causing its hyperexcitability and leading to peripheral sensitization (PS). In animal studies, peripherally injected rimabotulinumtoxinB blocks release of substance P from DRG and dorsal horn neurons and reduces dorsal horn neuronal activation (c-Fos) evoked by formalin injection (Marino et al. 2014). Furthermore, local trauma and ruptured disc initiate local accumulation of glutamate, a potent pain mediator, which also can enhance PS (Harrington et al. 2000). In the formalin model of pain, pretreatment of rat's paw with local administration of onaA (a week before formalin injection) significantly reduces local accumulation of glutamate and local

inflammation relieving the pain related to formalin application (Cui et al. 2004). In human, injection of five units of onaA into the temporalis muscle following introduction of 0.2 cc/1 mol of glutamate markedly reduces glutamate-generated pain within hours of administration (da Silva et al. 2014).

3. It has been shown that both development of inflammation in DRG and increased pain mediators within it are enhanced by extensive sprouting of sympathetic fibers into DRG after peripheral nerve injury (McLachlan et al. 1993), and sympathectomy or removal of sympathetic ganglia can reduce accumulation of inflammatory agents and pain mediators in DRG caused by disc protrusion (McLachlan and Hu 2014). In this regard, Rand and Whaler (1965) have shown that peripheral injection of onabotulinumtoxinA impairs sympathetic transmission and, hence, has the potential to reduce pain mediators and inflammatory agents.
4. The aforementioned effects of BoNTs can all reduce central sensitization (CS) via their primary suppressing effect on peripheral sensitization (PS). Moreover, intramuscular administration of onaA may reduce central sensitization via its suppressing effect on muscle spindle discharge (Filippi et al. 1993). Muscle spindles are one of the major sources of non-nociceptive input to the central nervous system reporting muscle length to CNS. In chronic pain disorders with established CS, wide range function spinal cord neurons perceive non-nociceptive stimuli as nociceptive (Robert 1968). Reducing the input from muscle spindles can reduce central sensitization.

Comment

Chronic low back pain is a complex disorder with heterogeneous causes and still poorly understood pathophysiology. The preliminary data, mainly from WRAMC studies, indicate that at least half of the patients with chronic low back pain, regardless of etiology, respond well to injection of onaA into erector spinae muscles. The technique uses 40 units at each of five lumbar levels (total of 200 units for one side). The 16-month follow-up study with three to four cycles of injection (using the same dose and technique) have supported the long-term efficacy of this technique, good patient tolerability, and safety of onaA treatment in chronic low back pain.

Although the investigators were worried about possible weakening effects of onaA in applied doses, none of the studied subjects in either of the two studies (blinded and open) complained of muscle weakness or impaired ambulation. However, the studied population in the WRAMC protocol included many (almost half) younger, muscular, and otherwise healthy military subjects with mechanical chronic low back pain. Therefore, the safety data in this study may not necessarily apply to older, thin, and fragile subjects with chronic low back pain; when treating such older, fragile patients, initial approach should be more conservative. The positive effect of WRAMC protocol was rated as C level of evidence (possibly effective) (one class II study) by AAN assessment subcommittee (Naumann et al. 2008).

The positive effect of onaA on cLBP is probably multifactorial pertaining to some the mechanisms outlined above.

The study of De Andres et al. (2010) showed only a trend of significance in the onaA group compared to the anesthetic and saline groups. The results of this study cannot be compared with that of the WRAMC protocol due to the significant differences between the two populations in regard to: (1) the study cohort (their patients all had MFPS with distinct trigger points) and (2) the injections pattern (QL and multifidus vs. ES injection in the WRAMC study), and (3) the total dose and number of sites injections (50 units total and 1 injection site versus 200 units with 5 injection sites in the WRAMC studies).

This author's experience with many patients whom he treated for chronic low back pain (mostly with onaA) during the past 15 years agrees with the results of WRAMC studies, i.e., approximately half of the patients report significant pain relief and marked improvement of quality of life (Video 5.1, patient interview). Video 5.2 demonstrates EMG-guided BoNT-A injection in the patient of Video 5.1. Much work still needs to be done in the area of cLBP with BoNTs. Due to the heterogeneity of chronic low back pain's etiology, future studies should focus on etiologically distinct subgroups of cLBP. Perhaps, it would be advantageous to use WRAMC's protocol first in such studies since it has already shown some promise in this area.

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