The Role of Botulinum Toxins in Treatment of Brain and Spinal Cord Injury Symptoms

Taraneh Hashemi-Zonouz and Bahman Jabbari

Traumatic brain injury (TBI) occurs as a result of blunt or penetrating head trauma and presents with a broad spectrum of symptoms and disabilities [1, 2]. TBIs constitute a major cause of death and critical public health around the world. The severity of TBI correlates with a significant social and financial burden with more than $1 billion dollars per year spending on hospitalizations [3]. The overall prevalence of TBIs for individuals between 0 and 25 years is 31–44% [4–6]. An increasing rate of road traffic injuries has resulted in rising numbers of traumatic brain injuries [7–9]. Annually, approximately 1.7 million people experienced some degree of TBI in the United States and 1.4 million of these injuries result in hospitalizations, 52,000 deaths, and 124,000 disabilities [1, 10]. Improved management of acute TBI has decreased the fatality rate, but has also caused a concomitant increase in the number of patients living with TBI-related disabilities [11]. Falls are the most common cause of TBI-related emergency department visits, while TBI-related deaths are mostly due to motor-vehicle accidents [12, 13].

This chapter discusses three symptoms of post-traumatic brain injury—spasticity, pain (including headaches), and post-traumatic movement disorders with a potential for improvement by botulinum toxin treatment.

T. Hashemi-Zonouz, M.D. (✉)
Radiology and Biomedical Imaging, Yale University, New Haven, CT, USA
e-mail: Taraneh.hashemi-zonouz@yale.edu; Taran.hz@gmail.com

B. Jabbari, M.D., FAAN
Department of Neurology, Yale University, New Haven, CT, USA
e-mail: bahman.jabbari@yale.edu

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Spasticity

Spasticity is defined as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome [14]. The exact pathophysiology of spasticity is still unclear. Jean-Michael Gracies discussed the likely and unlikely mechanisms responsible for development of spasticity in a recent comprehensive review [15, 16]. Decreased reciprocal Ia inhibition (which inhibits alpha motor neurons via a disynaptic interneuron) decreased non-reciprocal Ib inhibition and hyperexcitability of small group II afferents (originating from muscle spindle secondary endings) have been noted as possible mechanisms. The acute effects of TBI include paresis and short-term immobilization, whereas chronic effects result from plastic rearrangements in the CNS as the result of CNS injury, chronic disuse, or both. Changes in muscle innervation and reflex arch cause spasticity, spastic dystonia, and spastic co-contractions. Chronic spasticity and muscle disuse lead to contractures, which is often associated with significant disability. The TBI Model Systems National Database identified 75,000–100,000 annual cases of severe spasticity in U.S. [17], of which as high as 85% may develop contractures.

Although mild spasticity may not require treatment, moderate to severe spasticity often interferes with the individual's daily function [18, 19] and requires treatment. Treatment is aimed at reducing muscle tone, improving function and quality of life as well as preventing development of contractures. The currently available treatments for spasticity include: (1) pharmacological therapy combined with physical therapy and rehabilitation. Among pharmacological agents, baclofen, tizanidine, and diazepam are commonly used either as a single agent or in combination. Unfortunately, most patients with severe spasticity require high doses of these medications, which cause disturbing side effects such as sedation, mental changes, and dizziness. (2) For severe focal spasticity, injection of neurolytic nerve blocker phenol and/or anesthetic nerve blocks such as procaine and lidocaine are recommended [17, 20]. (3) In disabling spasticity, baclofen pump is helpful and can markedly reduce the spasticity [21]. Insertion of the baclofen pump, however, requires a dedicated setting and special expertise. Overdosing and withdrawal symptoms occur and can lead to serious side effects such as seizures and suppressed level of consciousness. (4) Corrective orthopedic surgery.

Botulinum Toxin Therapy

Over the past ten years, treatment of stroke-related spasticity with BoNT injections has been studied by several high-quality clinical trials [15, 22]. The positive results of these studies led to approval of botulinum toxin therapy for upper limb spasticity

by FDA in 2010 and 2015 (extended approval for including additional muscles) and for lower limb spasticity in 2016.

The literature on clinical trials of botulinum toxin therapy in spasticity caused by traumatic brain injury is limited to eight publications (Table 1). Five studies have a double blind-parallel design, one is double blind-crossover and two are open label. All five double blind-parallel studies have a mixed cohort, mostly stroke with TBI subjects comprising a much smaller proportion in the cohort. One small double blind and crossover and two small open label clinical trials are conducted exclusively on subjects with traumatic brain injury (Table 1).

The largest study conducted by Gracies et al. [23] assessed the efficacy of two doses of abobotulinum toxinA in a cohort consisting of 238 subjects with stroke and 23 subjects with TBI. This study showed that both low and high doses of aboA reduce muscle tone significantly and significantly improved the scores of Patient Global Assessment (PGA) (P's < 0.05). The patient Disability Assessment Scale (DAS) also improved, but the values did not reach statistical significance (0.07). The study of Barbaud et al. [24], which was conducted on 23 patients with TBI (double blind crossover), demonstrated that injection of 1000 units of aboA significantly improves spasticity, range of movement of ankle invertors and extenders as well as improving, to some extent, the gait velocity (Table 1). Significant improvement of the range of motion was also noted in another study that used 20–40 units of onaA per spastic muscles [25]. The study of Simpson et al. [26] compared the effect of onaA injections (maximum 500 units) in the upper extremity muscles of patients with TBI and stroke with the effect of tizanidine and placebo. OnaA was significantly better than tizanidine and placebo in reducing the muscle tone as well as improving the DAS score. Regarding side effects, one study mentioned that 10 out of 238 subjects experienced mild transient weakness after aboA injection (three in low-dose and seven in high-dose group) [23]. Transient local swelling and local pain at the site of injection were noted in two other patients [24, 25].

Comment

Using the guidelines of the American Academy of Neurology [27], the clinical trials using type A botulinum neurotoxin (aboA and onaA) for spasticity caused by TBI indicate efficacy (level B evidence) in reducing muscle tone, improving the range of motion, and attaining positive scores in physician global assessment (PGA) (one Class I and three class II studies). For rimaB, the level of evidence in C (possibly effective) is based on one class II study. One problem with the larger studies is that the number of TBI patients in the mixed cohort is too small. Assessment of disability and quality of life requires conduction of studies geared to specific evaluations in these areas of concerns.

Table 1 Clinical trials with BoNTs in patients with spasticity caused by Traumatic Brain Injury (TBI)

Author(s)	Study design	N and diagnosis	Limb	Toxin	Dose (U)	Result
Gracies et al. 2015 [23]	Double blind, parallel	238: Stroke 215 TBI 23	Upper	aboA	500, 1000	Mean change in MAS −0.3, −1.2, and −1.4 for placebo, 500 and 1000 toxin groups, respectively ($P < 0.0001$). Mean change in PGA score: 0.6, 1.4, and 1.8 for placebo, 500 and 1000 groups ($P = 0.0003$), ($P = 0.0001$). DAS reduction −0.5, −0.7, −07, placebo, 500 and 1000 groups (0.077) SE: mild transient hand weakness, 3 and 7 pts
Fietzek et al. 2014 [28]	Double blind, parallel	52: Stroke 35 Hypoxia 11 TBI 6	Lower	onaA	230–460	At week 12, MAS scores improved significantly in the onaA group compared to placebo ($P = 0.01$) SE: None
Gracies et al. 2014 [29]	Double blind, parallel	24: Stroke 19 TBI 5	Upper	rimaB	5000, 10,000, 15,000 Into each elbow flexor	Both doses improved elbow extension +8.3° ($P = 0.28$). Higher dose improved subject-perceived stiffness ($P = 0.05$). Subjective global self-assessment on pain, stiffness, and function also improved ($P = 0.17$) SE: None
Simpson et al. 2009 [26]	Double blind, parallel Comparator AboA/ tizanidine/ placebo	60: Stroke 49 TBI 11	Upper	onaA	500 (Max dose). All: 50 U into wrist flexors and extensors	Greater tone reduction in Ashworth scale with onaA compared to tizanidine or placebo ($P < 0.001$ and $P < 0.02$). Greater improvement in the cosmesis domain of DAS at week 6 ($P < 0.01$) SE: No focal weakness with onaA. SE higher with tizanidine (onaA and placebo the same)

(continued)

Table 1 (continued)

Author(s)	Study design	N and diagnosis	Limb	Toxin	Dose (U)	Result
Smith et al. 2000 [30]	Double blind, parallel	23: Stroke 21 TBI 2	Upper	aboA	500, 1000, 1500	Significant reduction of spasticity in MAS; significant increase in passive range of movements at the wrist, modest improvement at the elbow; significant improvement in patient global assessment (PGA); no change in upper limb disability scale
Pavesi et al. 1998 [31]	Open label	6: All TBI	Upper	onaA	90–100	Ashworth scale improved. One patient by 3°, two patients by 2°, and one patient by 1°. Three patients showed functional improvement (one writing, one using utensils, one dressing) SE: None
Burbaud et al. 1996 [24]	Double blind, crossover	23: All TBI	Lower	aboA	1000	Subjective improvement of foot spasticity ($P = 0.004$). Ankle invertor and extensors improved in MAS ($P = 0.001$ and 0.002). Modest improvement of gait velocity ($P = 0.071$) Less effective if spasticity had longer duration ($P = 0.008$) SE: transient local pain
Yablon et al. 1996 [25]	Open label	21: All TBI	Upper	onaA	20–40 per muscle	Mean passive range of motion improved 42.92° and 36.2° at 4 and 8 weeks ($P < 0.001$). Mean MAS rating improved 1.5 and 1.47 ($P = 0.01$ and 0.02) SE: one patient local swelling

OnaA botulinumtoxinA (Botox), *aboA* botulinumtoxinA (Dysport), *rimaB* rimabotulinumtoxinB (My bloc), *MAS* modified Ashworth scale, *DAS* disability assessment scale, *PGA* patient global assessment, *SE* side effects, *N* = number of patients

Pain in Post-traumatic Brain Injury

TBI-related pain and painful muscle spasm can be either neuropathic due to dysfunction of the nervous system or nociceptive as a result of damage to the musculoskeletal or visceral systems. A combination of both is also possible, depending on the extent and the level of the lesion. Furthermore, physiological and psychological factors may complicate pain sensation [32]. In the early phases of severe brain injury, affected individuals may experience very rigid and painful body postures. The strong subjective component of pain in TBI may complicate the design of effective drug therapies. Pain can arise from the brain, spinal cord, or even peripheral structures [33, 34]. TBI patients with severe spasticity often have pain associated with spasticity and, in carefully selected patients, release of muscle contractures can relief the pain [35]. A comprehensive review of RCTs published on the subject of chronic pain in TBI disclosed a prevalence of 51.5 among civilians and 43.1 among veterans [36]. Pain was more prevalent in patients with mild and moderate brain injury, although the reason for it was not clear.

Spasticity and contractures, common symptoms of chronic TBI, are often associated with pain. Jabbari reviewed the reported literature on the effect of botulinum toxin therapy on spasticity-associated pain regardless of the etiology [37]. Five of nine clinical trials reported significant improvement of pain, while four did not. The positive studies were more recent and used better pain scales. The effect of BoNT therapy on the pain associated with TBI-related spasticity needs exploration. Of the eight studies cited above (Table 1), only one [29] mentioned improvement of pain in three patients. However, it is not known whether three patients had TBI or stroke (mixed cohort).

Post-traumatic Headache (PTM)

Post-traumatic headache (PTH) is described as the headache that develops within 1 week after head trauma or within 1 week after regaining consciousness [38]. Approximately, 2% of the US population is disabled by post-traumatic headaches [37]. Headache is reported in nearly 93% of athletes after sports-related concussion [39]. Approximately, 81% of US service members report post-traumatic headaches [40, 41]. The most common patterns of PTH are migraine or probable migraine and tension-type headaches; migraine-type headaches are more prevalent [42]. PTH frequently has a persistent nature, which challenges its treatment. Besides analgesics and physical therapy, patients may benefit from a comprehensive psychological and cognitive therapy [38].

Botulinum toxin therapy is a major line of treatment for chronic migraine. The treatment improves migraine intensity and frequency and patients' quality of life. Long-term follow-up has proved its efficacy over several years and the safe profile of BoNT therapy in chronic migraine (for more detail in this subject, see Chap. 9 of this book). Yerry et al. [43] reported the result of botulinum toxin therapy with

onabotulinumtoxinA in 64 service members suffering from post-traumatic chronic migraine in a real-time retrospective consecutive case series. Blast injury was the most common type of trauma and was the cause in 56% of the patients. The mean age of the patients in the cohort was 31 years. The mean time from injury to the first onaA injections was 10.8 months. The injection protocol was the one recommended by the PREEMPT study group for treatment of chronic migraine [44]. After a single injection, 64% of the patients reported significant improvement of headaches. Two patients withdrew from the study due to side effects. The positive results of this study in PTM are encouraging. Proof of efficacy of BoNT treatment in post-traumatic migraine requires confirmation by controlled studies.

Post-traumatic Brain Injury and Involuntary Movement Disorders.

The history of botulinum toxin therapy began in the area of movement disorders and movement disorders continue to be major indications for this form of treatment [45]. Traumatic brain injury, similar to other forms of brain injury, can cause a variety of movement disorders such as dystonia, tremor, chorea, ballism, and tics [46]. Krauss et al. [47], followed 221 patients with severe traumatic head injury (Glascow score of <8) for 5 years and found that 50 patients (22.6%) developed involuntary movement disorders. The movements were transient in 10.4% and persistent in 12.2%. Forty-two patients (19%) had tremors which in 12 of them (5.4%) had a low frequency (2.5–4 Hz) and were disabling. Nine patients (4.1%) had dystonia which developed with a latency of 2 months to 2 years and seven (3.2%) had other movement disorders. In a later study, the same authors found a prevalence of 10.1% for involuntary movements in a cohort of 158 patients with mild to moderate head injury. Persistent movement was noted in 2.6% of this cohort [48].

Treatment with BoNTs is rarely reported for movement disorders caused by traumatic brain injury. Kemp et al. [49] reported a 42 year-old man who following a motor bike accident sustained a severe TBI. Six months later, he developed involuntary, action-induced dystonic posturing of the left leg, which interfered with ambulation. When attempted to ambulate, the left foot assumed a dorsiflexion posture and the whole leg extended. Injection onabotulinumtoxinA (Botox) into the left quadriceps (200 units) and left gastrocnemius (50 medial, 25 lateral) resulted in marked improvement of involuntary movement and helped ambulation. The case described below is from our experience with a patient who suffered from post-traumatic hemibalismus.

Case Report

A 74-year-old man, within days following a car accident, developed continuous ballistic movements of the left side, more prominent in the left upper extremity. A computerized tomography scan demonstrated an area of intracerebral hemorrhage affecting the left globus pallidus. His examination showed mild left hemiparesis and

hyperreflexia. The left upper limb displayed high amplitude continuous movements consisting of forceful flexion and extension of the elbow, adduction/abduction of the left arm, left shoulder elevation, and wrist extension. Treatment with baclofen, diazepam, anticholinergic, and muscle relaxants was not helpful. The patient was exhausted 3 days after the onset of the movements. OnabotulinumtoxinA was injected into the following muscles on the left side: trapezius, triceps, biceps, and pectoralis each 100 units; Deltoid 50 units. Forty-eight hours following treatment with onaA, patient's movement showed marked reduction in amplitude and intensity. The treatment enables him to rest and sleep and get through the acute phase of the movements. The patient's examination 3 months later showed mild left hemi-chorea and a subtle left hemiparesis.

Traumatic Spinal Cord Injury

The National Spinal Cord Injury Statistics Center report in 2014 gives an estimate of 273, 000 cases of traumatic SCI in the US and an incidence of 12,000/year for traumatic SCI [50]. Traumatic spinal cord injury is the cause of a variety of major health problems. High-quality clinical trials have shown that treatment with BoNTs is efficacious in spasticity, bladder dysfunction, and pain disorders in a variety of medical conditions. Patients with traumatic spinal cord injury also often suffer from these three disorders. This section discusses the role of botulinum toxin therapy for management of spasticity, bladder dysfunction, and pain in traumatic SCI. In one report, 85% of the patients with severe spasticity caused by SCI demonstrated notable improvement with baclofen pump and 65% of them have shown reduction of muscle spasm frequency [51]. Treatment with the pump, however, needs special setting and technical expertise to avoid overdosing and dealing with withdrawal issues.

Spasticity

Spasticity affects approximately 70% of the patients with spinal cord injury and can be the cause of significant disability [52]. Holtz et al. followed 465 patients with spinal cord injury for 10 years through a prospective registry [53]. After trauma, 65% of the patients demonstrated some degree of spasticity. Spasticity was "problematic" and interfered with functioning in 35% of the patients. At 1-, 2-, and 5-year period after spinal cord trauma, 27%, 24%, and 20% of the patients, respectively, reported significant interruption in daily activities by spasticity. Mild spasticity may not require treatment. Moderate or severe spastic limbs, however, interfere with motor function and, in case of lower limbs, with ambulation.

Botulinum toxin treatment of Spasticity resulting from traumatic SCI. The literature on this area is surprisingly scarce compared to treatment of spasticity with

BoNTs in traumatic brain injury. No high-quality clinical trials exist. There are a number of retrospective and prospective open label observations with reports in small number of patients (Table 2). These studies collectively suggest that BoNTs improve spasticity of traumatic spinal cord injury and the quality of life in the affected patients, a conclusion that is also supported by a handful of case reports.

Bladder Problems in Traumatic SCI

Micturition is controlled by sacral (S2-S4) center (SC) and pontine micturition center (PMC) with participation of cerebral cortex [57]. However, trauma or lesions in other spinal cord regions can also interfere with micturition via involvement of

Table 2 Clinical trials assessing the efficacy of BoNTs in spasticity caused by traumatic SCI

Author(s)	Design	*N*	Toxin	Dose	Injection	Results
Opera et al. 2007 [54]	Pros Open Label	8	onaA	100–400	Hip adductors knee flexors Foot flexors	Three weeks after injection: Decreased MAS ($P < 0.001$) and pain in VAS ($P < 0.02$) Increased RFI ($P < 0.003$) and MRMI ($P < 0.003$)
Marciniak et al. 2008 [55]	Retros Open Label	28	onaA	50–500	Large number of proximal and distal flexors and extensors	Improvement of upper limb function (78%) Improvement of hygiene (67%) Improvement of ambulation (56%)
Bernuz et al. 2012 [56]	Pros Open Label	15	onaA	200	Rectus femoris	Three weeks after injection: Increase gait velocity, swing phase and Stride length ($P < 001$). MTD angle and grade improvement ($P < 0.05$) Reduced walking discomfort
Spiegel et al. 2014 [50]	Pros Open Label	9	onaA	800–2000	Six muscles in lower limbs	At 2 weeks, significant reduction of spasticity (two points or more on Ashworth scale) in six of nine patients Five of nine patients reported significant functional improvement (Transfers, getting in and out of wheelchair, etc.)

Pros prospective, *Retros* retrospective, *MST* Modified Tandieu Scale, *MAS*: modified Ashworth Scale, *MRMI* modified Rivermead mobility index, *RFI* functional index

descending motor and autonomic fibers. Traumatic spinal cord injury causes a variety of voiding problems including overactive and underactive bladder and voiding problems related to detrusor and sphincter muscle communication. Neurogenic detrusor overactivity (NDO) and detrusor-sphincter dys-synergia (DSD) are common complications of traumatic spinal cord injury. Both conditions can cause disturbing symptoms such as urinary urgency, incontinence and intermittent urinary retention as well as predisposing the patients to urinary tract to infection. Anticholinergic drugs are commonly used to alleviate the symptoms of NDO, but are often poorly tolerated in the older patients. The symptoms of NDO, OAB (idiopathic overactive bladder), and DSD are described in more detail in Chap. 4 of this book entitled Applications of Botulinum Toxin in the Urinary Tract.

Treatment of Bladder Problems Caused by Traumatic SCI with BoNTs

Most studies conducted to prove the efficacy of BoNTs in NDO have been in cohorts that comprise more than one etiology. In each large study cohort, however, a substantial number consists of patients with traumatic SCI (Table 3). These investigations demonstrate several important points: (1) The evidence-based data from these studies justifies assignment of level A efficacy [27] (effective due to two or more class I studies) for BoNT therapy to NDO caused by traumatic SCI. (2) The efficacy of BoNTs on the NDO of SCI is comparable with the onaA effect upon the NDO caused by other etiologies (i.e., multiple sclerosis). In other words, BONT therapy improves NDO regardless of etiology. (3) The effect of BoNTs on the NDO of SCI is independent of anticholinergic therapy. The FDA based on the results of multicenter studies approved the use of onabotulinum toxin A for treatment of NDO in 2011 and for treatment of idiopathic overactive bladder (OAB) in 2013.

A recent retrospective review of 211 patients comparing the results of 750 units of aboA with 200 units of onaA injected into detrusor muscle for NDO claims a higher rate of success with aboA (66% versus 41%) in patients with spinal cord injury. This finding requires verification by future controlled studies [58].

The optimal technique of injection is still a matter of debate. The FDA's approved dose for onaA treatment of NDO is a total of 200 units into 30 injection sites, sparing the bladder's trigon. However, some authorities in the field prefer trigon injection due to the abundance of nerve fibers in this area [59]. Emerging data also suggests that smaller doses between 100 and 150 may be sufficient at least in some cases of NDO and, in case of abobotulinumtoxinA treatment, recent data in both human and animals suggest that 15 injection sites are sufficient to produce desirable effects [60, 61].

Table 3 Major clinical studies launched to assess the role of botulinum toxin therapy on NDO of patients with traumatic brain injury

Authors	Design	*N*	Type	Toxin	Dose (unit)	Results
Denys et al. 2016 [61]	Double blind placebo-controlled	47 SCI and MS SCI?	NDO	aboA	750 U Detrusor 15 injections 30 injections	Maximum cystometric capacity, maximum detrusor pressure and volume at first contraction improved the Dysport groups compared with placebo ($P < 0.05$). 15 injection sites as effective as 30 Quality of life improved
Hui et al. 2016 [69]	Single blind comparator	91 SCI	NDO	onaA	1–200 into detrusor 2–1600 into detrusor + 40 into trigon	At 12 weeks the group with combined injection did better on QoL scale, mean urinary incontinence episodes, complete dryness (mean voiding volume (159.72 vs. 139.07 ml, $P = 0.02$)), VFIDC with improvement of the duration of first detrusor contraction and the number of patients with detrusor contraction—All *P* values <0.05
Sussman et al. 2013 [70]	Double blind placebo-controlled	183 SCI and MS	NDO	onaA	200 Detrusor 300 Detrusor	Both groups faired significantly more than placebo at 6 and 12 weeks in regard to several quality of life measures: I-QOL, HRQoL, 16-item modified Overactive Bladder-Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ), Patient Global Assessment ($P < 0.05$)

(continued)

Table 3 (continued)

Authors	Design	*N*	Type	Toxin	Dose (unit)	Results
Reitz et al. 2004 [76] European	Retrospective Multicenter	200 SCI and MS 165 SCI	NDO	onaA	300 Detrusor	Increased mean bladder capacity and mean bladder compliance ($P < 0.001$), increased mean reflex volume ($P < 0.01$), decreased mean voiding pressure ($P < 0.001$). Patient reduced anticholinergic, some even stopped
Cruz et al. 2011 [74]	Double blind placebo-controlled	275 SCI and MS 121 SCI	NDO	onaA	200 300 Placebo	UI episodes decreased in toxin groups ($P < 0.01$) Quality of life measured by I-QoL significantly improved in toxin groups at week 6 Side effects—urinary infection and retention
Ginsberg et al. 2012 [73]	Double blind placebo-controlled	414 189 SCI	NDO	onaA	200 300 Placebo	Reduced UI frequency, improved incontinence quality of life score, prolonged median time to patient retreatment request ($P < 0.001$)
Ginsberg et al. 2013 [71]	Pooled data on two double blind studies	691 SCI and MS 310 SCI	NDO	onaA	200 300 Placebo	Toxin group 50% or more reduction in UI episodes. Maximum detrusor pressure, maximum cytometric capacity, detrusor contraction and quality of life all improved in the toxin group. No difference between 200 and 300 dose

(continued)

Table 3 (continued)

Authors	Design	*N*	Type	Toxin	Dose (unit)	Results
Chancellor et al. 2013 [72]	Double blind placebo-controlled	417 189 SCI	NDO	onaA	200 300 Placebo	Focus on quality of life—Measures of I-QoL, patient satisfaction with treatment questionnaire (OAB-PSTQ and Patient Global Assessment (PGA)) all significantly better in toxin groups compared to placebo ($P < 0.001$)
Herschrom et al. 2011 [75]	Double blind placebo-controlled	57 SCI and MS	NDO	onaA	300 Placebo	At week 6, marked reduction of UI and improvement of quality of life

I-QoL incontinence quality of life, *HRQoL* health-related quality of life, *OAB-PSTQ* 16-item modified overactive bladder-patient satisfaction with treatment questionnaire, *UI* urinary frequency, *NDO* neurogenic detrusor overactivity, *N* number

Detrusor-Sphincter Dys-synergia

In this condition, co-contraction of detrusor and sphincter muscles interferes with normal urination. It can be simply classified as intermittent or continuous depending on the pattern of sphincter's EMG activity [62]. Chronic DSD has a potential to cause renal failure, hence early treatment is advisable. Approximately 20–25% of patients with multiple sclerosis develop DSD, but the true incidence of DSD in traumatic SCI (although suspected to be high) is not known.

A few uncontrolled studies have suggested the efficacy of BoNT injection into the urethral sphincter for DSD caused by traumatic spinal cord injury (Table 4). The preliminary data on the effect of urethral injection of onabotulinum toxin A for DSD in traumatic SCI is promising, but proof of efficacy requires data from placebo-controlled studies.

Pain After Traumatic Spinal Cord Injury

Chronic pain is a common finding after spinal cord injury. In a recent study of 537 patients with traumatic spinal cord injury, 76% of the subjects reported chronic pain and in 60% pain was identified as neuropathic pain. The pain was characterized as severe in 28.1% of the patients. In the same cohort, 71% of the patients demonstrated spasticity in the examination [63].

The two major categories of pain after cord injury consist of neuropathic and nociceptive types. The former occurs following specific damage to neural tissue and

Table 4 Clinical trials on the efficacy of intraurethral sphincter injections of onabotulinum toxinA (onaA) for DSD caused by traumatic SCI

Author	Design	*N*	Toxin	Dose	Result—improvement	Side effect
Schurch et al. 1996 [77]	Open label	24	onaA	100 U	21 of 24 patients demonstrated significant improvement of symptoms. Effects lasted 3–9 months	Side efects never occurred
De Seze et al. 2002 [78]	Randomized, DB—onaA versus Lidocaine	13	onaA	100 U	onaA group showed significant decrease in PRUV and MAUP at days 7 and 30 compared to lidocaine (*P* values <0.01 and <0.04), respectively No improvement of MVP	Transitory exacerbation of preexisting urinary incontinence for 2 weeks (one patient)
Kuo 2008 [79]	Open label	50	onaA	100 U	78% satisfaction with treatment Voiding detrusor pressure ($P = 0.016$) Maximum flow rate ($P = 0.047$) Post-void residual volume ($P = 0.025$) IL-O-7 Score ($P = 0.025$)	Increase in incontinence

PRUV post-voiding residual urine volume, *MUP* maximum urethral pressure, *MVP* maximum voiding pressure, *onaA* onaboulinumtoxinA (Botox)

somatosensory system, whereas the latter arises from the musculoskeletal damage. Neuropathic pain often has a burning or searing quality and includes dermatomal allodynia. The pain can manifest above the level of injury, at the level of injury, or below the level of injury [64]. Pain at the level of injury is often associated with signs and symptoms of nerve root injury.

A recent review [65] of pharmacologic of treatment of NP after spinal cord injury identified 35 clinical trials in this area. According to this review, the evidence-based information justifies level 1 efficacy (high) for lidocaine, tramadol, gabapentin, and pregabaline for treatment of neuropathic pain after spinal cord injury, while a level 2 evidence is assigned to lomotrigine. There is level 1 evidence that amitriptyline and venlafaxine are effective in reducing NP, but only in patients with depression. There is level 1 evidence that mexelitine, levetiracetam, trazadone, and duloxetine are not effective in NP caused by traumatic SCI. The evidence for efficacy of cannabinoids for NP occurring after traumatic SCI is controversial.

In 1994, we have reported a women with intramedullary hemangioma at C7 level who suffered from severe neuropathic pain and disabling T1 dermatome allodynia

[66]. Injection of onaA into the allodynic dermatomes resulted in marked improvement of the pain and allodynia (see more detailed description of this case in Chap. 9, under central neuropathic pain). Han et al. [67] first reported significant improvement of neuropathic pain after spinal cord injury in a 51 year-old man who had suffered from C3 AIS B (American Spinal Cord Injury Association scale B) tetraplegia. Authors injected 10 units of onabotulinumtoxinA subcutaneously into the ten most painful areas of each sole. In 2016, the same group of authors reported on a randomized double blind, placebo-controlled study which investigated the effect of subcutaneous onabotulinumtoxinA injection in 40 patients with neuropathic pain after traumatic spinal cord injury [68]. Authors injected 200 units of onaA into the painful areas in a grid-like pattern and evaluated the response at 4 and 8 weeks with VAS, McGill pain questionnaire, and the WHO version of brief quality of life assessment (WHOQoL-BREF). At 4 and 8 weeks after injection, the VAS score for pain was significantly reduced by 18.6 ± 16.8 and 21.3 ± 26.8, respectively, in the toxin groups, whereas it was reduced by 2.6 ± 14.6 and 0.3 ± 19.5, respectively, in the placebo group ($P < 0.002$ and $P < 0.005$). A pain relief of >20% occurred in 55% and 45% (4 and 8 weeks) of the toxin group compared to 15% and 10% of the placebo group. Physical health domain of the WHOQOL-BREF also improved in the onaA group ($P = 0.052$).

Pain in traumatic SCI can also be associated with spasticity. In a retrospective study of 28 patients with traumatic spinal cord injury and spasticity, Marciniak et al. reported that treatment of spasticity with onabotulinumtoxinA improved the pain associated with spasticity in 81% of the patients [55].

Conclusions of the Section on Traumatic SCI

The efficacy of botulinum therapy (with onaA) in the neurogenic detrusor over activity (NDO) caused by SCI has been established via high-quality clinical trials. Further refinement of the technique of injection will provide better yield and more comfort to the patients. Subcutaneous injection of onabotulinum toxin A probably relieves the neuropathic pain caused by spinal cord injury (one class I study), but more RCTs are needed since the magnitude of response was modest (20%) in that single class I trial [68]. The positive findings regarding treatment of spasticity of SCI with BoNTs are all from class VI (retrospective) studies (Table 2); hence, the proof of efficacy should await availability of data from high-quality RCTs.

References

1. Lagbas C, et al. Traumatic brain injury related hospitalization and mortality in California. Biomed Res Int. 2013;2013:143092.
2. Thurman DJ, et al. Traumatic brain injury in the United States: a public health perspective. J Head Trauma Rehabil. 1999;14(6):602–15.

3. Schneier AJ, et al. Incidence of pediatric traumatic brain injury and associated hospital resource utilization in the United States. Pediatrics. 2006;118(2):483–92.
4. McKinlay A, et al. Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. Brain Inj. 2008;22(2):175–81.
5. Segalowitz SJ, Brown D. Mild head injury as a source of developmental disabilities. J Learn Disabil. 1991;24(9):551–9.
6. Body C, Leathem J. Incidence and aetiology of head injury in a New Zealand adolescent sample. Brain Inj. 1996;10(8):567–74.
7. Roozenbeek B, Maas AIR, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013;9(4):231–6.
8. Patel A, et al. Quality of the development of traumatic brain injury clinical practice guidelines: a systematic review. PLoS One. 2016;11(9):e0161554.
9. Song SY, et al. Analysis of mortality and epidemiology in 2617 cases of traumatic brain injury: Korean Neuro-Trauma Data Bank System 2010–2014. J Korean Neurosurg Soc. 2016;59(5):485–91.
10. Faul M, et al. Traumatic brain injury in the United States. Atlanta, GA: National Center for Injury Prevention and Control, Centers for disease Control and Prevention; 2010.
11. Marshall LF. Head injury: recent past, present, and future. Neurosurgery. 2000;47(3):546–61.
12. Coronado VG, et al. Surveillance for traumatic brain injury-related deaths: United States, 1997–2007. US Department of Health and Human Services, Centers for Disease Control and Prevention: Atlanta; 2011.
13. Coronado VG, et al. Trends in traumatic brain injury in the US and the public health response: 1995–2009. J Saf Res. 2012;43(4):299–307.
14. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. Muscle Nerve. 2005;31(5):535–51.
15. Moeini-Naghani I, Hashemi-Zonouz T, Jabbari B. Botulinum toxin treatment of spasticity in adults and children. Semin Neurol. 2016;36(1):64–72.
16. Gracies JM. Pathophysiology of spastic paresis. II: emergence of muscle overactivity. Muscle Nerve. 2005;31(5):552–71.
17. Schindler-Ivens S, Shields RK. Low frequency depression of H-reflexes in humans with acute and chronic spinal-cord injury. Exp Brain Res. 2000;133(2):233–41.
18. Heckman CJ, Gorassini MA, Bennett DJ. Persistent inward currents in motoneuron dendrites: implications for motor output. Muscle Nerve. 2005;31(2):135–56.
19. Kitzman P. Alteration in axial motoneuronal morphology in the spinal cord injured spastic rat. Exp Neurol. 2005;192(1):100–8.
20. Bose P, Hou J, Thompson FJ. Traumatic brain injury (TBI)-induced spasticity: neurobiology, treatment, and rehabilitation. In: Kobeissy FH, editor. Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects. Boca Raton, FL: CRC Press/Taylor & Francis; 2015.
21. Bose P, et al. Effects of acute intrathecal baclofen in an animal model of TBI-induced spasticity, cognitive, and balance disabilities. J Neurotrauma. 2013;30(13):1177–91.
22. Brown EA, Schütz SG, Simpson DM. Botulinum toxin for neuropathic pain and spasticity: an overview. Pain. 2014;4(2):129–51.
23. Gracies J-M, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. Lancet Neurol. 2015;14(10):992–1001.
24. Burbaud P, et al. A randomised, double blind, placebo controlled trial of botulinum toxin in the treatment of spastic foot in hemiparetic patients. J Neurol Neurosurg Psychiatry. 1996;61(3):265–9.
25. Yablon SA, et al. Botulinum toxin in severe upper extremity spasticity among patients with traumatic brain injury an open-labeled trial. Neurology. 1996;47(4):939–44.
26. Simpson DM, et al. Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study. J Neurol Neurosurg Psychiatry. 2009;80(4):380–5.
27. Gronseth G, French J. Invited article: practice parameters and technology assessments what they are, what they are not, and why you should care. Neurology. 2008;71(20):1639–43.

28. Fietzek U, et al. Early botulinum toxin treatment for spastic pes equinovarus—a randomized double-blind placebo-controlled study. Eur J Neurol. 2014;21(8):1089–95.
29. Gracies J-M, et al. Botulinum toxin type B in the spastic arm: a randomized, double-blind, placebo-controlled, preliminary study. Arch Phys Med Rehabil. 2014;95(7):1303–11.
30. Smith S, et al. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. Clin Rehabil. 2000;14(1):5–13.
31. Pavesi G, et al. Botulinum toxin type A in the treatment of upper limb spasticity among patients with traumatic brain injury. J Neurol Neurosurg Psychiatry. 1998;64(3):419.
32. Siddall PJ, Finnerup NB. Pain following spinal cord injury. Handb Clin Neurol. 2006;81:689–703.
33. Pertovaara A. The noradrenergic pain regulation system: a potential target for pain therapy. Eur J Pharmacol. 2013;716(1):2–7.
34. Lemmens S, et al. Alpha-Adrenoceptor modulation in central nervous system trauma: pain, spasms, and paralysis—an unlucky triad. Med Res Rev. 2015;35(4):653–77.
35. Namdari S, et al. Shoulder tenotomies to improve passive motion and relieve pain in patients with spastic hemiplegia after upper motor neuron injury. J Shoulder Elb Surg. 2011;20(5):802–6.
36. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. JAMA. 2008;300(6):711–9.
37. Jabbari B. Botulinum toxin treatment of pain disorders. New York: Springer; 2015.
38. Lew HL, et al. Characteristics and treatment of headache after traumatic brain injury: a focused review. Am J Phys Med Rehabil. 2006;85(7):619–27.
39. Lenaerts ME. Post-traumatic headache: from classification challenges to biological underpinnings. Cephalalgia. 2008;28(1 suppl):12–5.
40. Seifert T. Post-traumatic headache therapy in the athlete. Curr Pain Headache Rep. 2016;20(6):1–9.
41. Holtkamp MD, Grimes J, Ling G. Concussion in the military: an evidence-base review of mTBI in US military personnel focused on posttraumatic headache. Curr Pain Headache Rep. 2016;20(6):1–6.
42. Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. Headache. 2010;50(8):1262–72.
43. Yerry JA, Kuehn D, Finkel AG. Onabotulinum toxin a for the treatment of headache in service members with a history of mild traumatic brain injury: a cohort study. Headache. 2015;55(3):395–406.
44. Blumenfeld A, et al. Method of injection of OnabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. Headache. 2010;50(9):1406–18.
45. Jabbari B. History of botulinum toxin treatment in movement disorders. Tremor Other Hyperkinet Mov. 2016;6:394.
46. Krause T, et al. Dantrolene—a review of its pharmacology, therapeutic use and new developments. Anaesthesia. 2004;59(4):364–73.
47. Krauss JK, Trankle R, Kopp K-H. Post-traumatic movement disorders in survivors of severe head injury. Neurology. 1996;47(6):1488–92.
48. Krauss JK, Tränkle R, Kopp KH. Posttraumatic movement disorders after moderate or mild head injury. Mov Disord. 1997;12(3):428–31.
49. Kemp S, et al. Delayed-onset focal dystonia of the leg secondary to traumatic brain injury. J Clin Neurosci. 2012;19(6):916–7.
50. Spiegl UJ et al. Antispastic therapy with botulinum toxin type A in patients with traumatic spinal cord lesion. GMS Interdiscip Plast Reconstr Surg DGPW 2014;3:Doc14.
51. Dario A, Tomei G. A benefit-risk assessment of baclofen in severe spinal spasticity. Drug Saf. 2004;27(11):799–818.
52. Gorgey AS, et al. Relationship of spasticity to soft tissue body composition and the metabolic profile in persons with chronic motor complete spinal cord injury. J Spinal Cord med. 2010;33(1):6–15.

53. Holtz KA, et al. The prevalence and effect of problematic spasticity following traumatic spinal cord injury. Arch Phys med Rehabil. 2016;98(6):1132–8.
54. Opara J, Hordyńska E, Swoboda A. Effectiveness of botulinum toxin A in the treatment of spasticity of the lower extremities in adults-preliminary report. Ortop Traumatol Rehabil. 2006;9(3):277–85.
55. Marciniak C, Rader L, Gagnon C. The use of botulinum toxin for spasticity after spinal cord injury. Am J Phys Med Rehabil. 2008;87(4):312–7. quiz 318–20, 329
56. Bernuz B, et al. Botulinum toxin effect on voluntary and stretch reflex-related torque produced by the quadriceps an isokinetic pilot study. Neurorehabil Neural Repair. 2012;26(5):542–7.
57. Goldmark E, Niver B, Ginsberg DA. Neurogenic bladder: from diagnosis to management. Curr Urol Rep. 2014;15(10):1–8.
58. Peyronnet B, et al. Intradetrusor injections of onabotulinum toxin A (Botox®) 300 U or 200 U versus abobotulinum toxin a (Dysport®) 750 U in the management of neurogenic detrusor overactivity: a case control study. Neurourol Urodyn. 2017;36(3):734–9.
59. Smith CP, Chancellor MB. Botulinum toxin to treat neurogenic bladder. Semin Neurol. 2016;36(1):5–9.
60. Denys P, et al. Efficacy and safety of two administration modes of an intra-detrusor injection of 750 units dysport®(abobotulinumtoxinA) in patients suffering from refractory neurogenic detrusor overactivity (NDO): a randomised placebo-controlled phase IIa study. Neurourol Urodyn. 2016;36(2):457–62.
61. Huynh Le Maux A, et al. Does reduction of number of Intradetrusor injection sites of abo-BoNTA (Dysport®) impact efficacy and safety in a rat model of neurogenic detrusor Overactivity? Toxins. 2015;7(12):5462–71.
62. Stoffel JT. Detrusor sphincter dyssynergia: a review of physiology, diagnosis, and treatment strategies. Transl Androl Urol. 2016;5(1):127.
63. Andresen SR, et al. Pain, spasticity and quality of life in individuals with traumatic spinal cord injury in Denmark. Spinal Cord. 2016;54(11):973–9.
64. Bryce TN, et al. International spinal cord injury pain (ISCIP) classification: part 2. Initial validation using vignettes. Spinal Cord. 2012;50(6):404–12.
65. Teasell RW, et al. A systematic review of pharmacologic treatments of pain after spinal cord injury. Arch Phys Med Rehabil. 2010;91(5):816–31.
66. Jabbari B, Maher N, Difazio MP. Botulinum toxin A improved burning pain and allodynia in two patients with spinal cord pathology. Pain Med. 2003;4(2):206–10.
67. Han ZA, Song DH, Chung ME. Effect of subcutaneous injection of botulinum toxin A on spinal cord injury-associated neuropathic pain. Spinal Cord. 2014;52:S5–6.
68. Han ZA, et al. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016;79(4):569–78.
69. Hui C, Keji X, Chonghe J, Ping T, Rubiao O, Jianweng Z, Xiangrong D, Liling Z, Maping H, Qingqing L, Qiuling L, Jiebing H, Tanghai H. Combined detrusor-trigone BTX-A injections for urinary incontinence secondary to neurogenic detrusor overactivity. Spinal Cord. 2015;54(1):46–50.
70. Sussman D, Patel V, Del Popolo G, Lam W, Globe D, Pommerville P. Treatment satisfaction and improvement in health-related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. Neurourol Urodyn. 2013;32(3):242–9.
71. Ginsberg D, Cruz F, Herschorn S, Gousse A, Keppenne V, Aliotta P, Sievert KD, Brin MF, Jenkins B, Thompson C, Lam W, Heesakkers J, Haag-Molkenteller C. Onabotulinumtoxin A is effective in patients with urinary incontinence due to neurogenic detrusor activity regardless of concomitant anticholinergic use or neurologic etiology. Adv Ther. 2013;30(9):819–33.
72. Chancellor MB, Patel V, Leng WW, Shenot PJ, Lam W, Globe DR, Loeb AL, Chapple CR. Onabotulinumtoxin A improves quality of life in patients with neurogenic detrusor overactivity. Neurology. 2013;81(9):841–8.
73. Ginsberg D, Gousse A, Keppenne V, Sievert K-D, Thompson C, Lam W, Brin MF, Jenkins B, Haag-Molkenteller C. Phase 3 efficacy and tolerability study of onabotulinumtoxina for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012;187(6):2131–9.

74. Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, Daniell G, Heesakkers J, Haag-Molkenteller C. Efficacy and safety of onabotulinumtoxina in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011;60(4):742–50.
75. Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care. 2011;17:S139–45.
76. Reitz A, Stöhrer M, Kramer G, Del Popolo G, Chartier-Kastler E, Pannek J, Burgdörfer H, Göcking K, Madersbacher H, Schumacher S, Richter R, von Tobel J, Schurch B. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol. 2004;45(4):510–5.
77. Schurch B, Hauri D, Rodic B, Curt A, Meyer M, Rossier AB. Botulinum-A toxin as a treatment of detruosor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients. J Urol. 1996;155(3):1023–9.
78. de Sze M, Petit H, Gallien P, de Sze M-P, Joseph P-A, Mazaux J-M, Barat M. Botulinum A toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol. 2002;42(1):56–62.
79. Kuo H-C. Satisfaction with urethral injection of botulinum toxin A for detrusor sphincter dyssynergia in patients with spinal cordlesion. Neurourol Urodyn. 2008;27(8):793–6.