The Use of Botulinum Toxin for Treatment of Spasticity

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Contents

Abstract

Spasticity is one component of the upper motor neuron (UMN) syndrome resulting from a multitude of neurologic conditions, such as stroke, brain injury, spinal cord injury, multiple sclerosis, and cerebral palsy. It is clinically recognized as a phenomenon of velocity-dependent increase in resistance, i.e., hypertonia. Recent advances in the pathophysiology of spasticity improve our understanding of mechanisms underlying this complex phenomenon and its relations to other components of UMN syndrome (weakness and disordered motor control), as well as the resultant clinical problems. This theoretical framework provides a foundation to set up treatment goals and to guide goal-oriented clinical assessment and treatment. Among a spectrum of treatment options, botulinum toxin (BoNT) therapy is the preferred treatment for focal spasticity. The evidence is very robust that BoNT therapy effectively reduces spasticity;

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however, it does not improve voluntary movement. In this chapter, we highlight a few issues on how to achieve the best clinical outcomes of BoNT therapy, such as dosing, dilution, guidance techniques, adjunctive therapies, early treatment, repeated injections, and central effects, as well as the ways to improve motor function in selected subgroups of patients with spasticity. We also discuss the reasons of poor responses to BoNT therapy and when not to use BoNT therapy.

Keywords
Botulinum toxin · Brain injury · Human · Motor recovery · Rehabilitation · Spasticity · Spinal cord injury · Stroke

1 Introduction

Spasticity is one component of the upper motor neuron (UMN) syndrome resulting from a multitude of neurologic conditions. Clinically, spasticity is easily recognized as a phenomenon of velocity-dependent increase in tonic stretch reflexes ("muscle tone") with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex (Lance 1980). Estimates of spasticity incidence and prevalence vary, due to the lack of a strict definition and clinical measurement of spasticity. It is estimated to occur in around 80% of persons with multiple sclerosis (Patejdl and Zettl 2017) and 65–78% in those with spinal cord injuries (Maynard et al. 1990). Prevalence in stroke is about 20–40% (Zorowitz et al. 2013). Within the first year of stroke, spasticity was found in 38% of survivors (Watkins et al. 2002). However, spasticity is present in 97% of chronic stroke survivors with moderate to severe motor impairments (Pundik et al. 2018). Presence of spasticity in persons with traumatic brain injuries (TBI) depends on the severity of injury. Spasticity can exist in up to 40% of those with severe brainstem involvement (Wedekind and Lippert-Grüner 2005).

Spasticity is significant because it not only causes problems directly, such as pain, distorted joint position, and posture and hygiene difficulties, but it also predisposes to other complications, such as joint contractures and permanent deformities. Furthermore, spasticity interacts with and amplifies the effects of other impairments, such as weakness, exaggerated stretch reflexes, clonus, impaired coordination, and motor control and planning, thus contributing to limitations in activity and participation (Mayer and Esquenazi 2003). These numerous abnormalities and impairments intersect and evolve over time, thus producing a dynamic picture of varying clinical presentations after an UMN lesion (Gracies 2005a, b). These interactions often result in abnormal joint postures, disordered motor control, and functional limitations, such as difficulty in grasping, reaching, walking, transferring, and performing hygiene, dressing, self-care, and other activities of daily living. In addition, spasticity-related stiffness and discomfort can interfere with these physical activities and contribute to psychological consequences on mood and self-esteem (Thompson et al. 2005). Collectively, these motor impairments limit their vocational and social participation in more than half of stroke survivors at age 65 and over (Murphy and Carmine 2012; Benjamin et al. 2017).

2 Pathophysiology and Clinical Presentations

The underlying mechanisms of spasticity are still poorly understood. This partly makes it a challenge for clinicians to understand the clinical presentations and problems and to develop a plan of care. Here we first briefly summarize current understandings of poststroke spasticity and its relation to clinical presentations and problems (Brown 1994; Gracies 2005b; Nielsen et al. 2007; Mukherjee and Chakravarty 2010; Burke et al. 2013; Stecco et al. 2014; Li and Francisco 2015) (Fig. 1). A stroke often damages the motor cortex and its descending corticospinal tract (CST), immediately causing muscle weakness (usually unilateral), subsequently resulting in incoordination and often joint immobilization. On the other hand, neuroplastic changes occur after stroke as well. Due to lesions of corticobulbar pathways accompanied with lesion of motor cortices and/or descending CST, bulbospinal hyperexcitability gradually develops due to loss of cortical inhibition. This is mainly a phenomenon of disinhibition or unmasking effects. Potential candidates include reticulospinal, vestibulospinal, and rubrospinal projections (Miller et al. 2014; Li and Francisco 2015; Owen et al. 2017). Medial reticulospinal (RS) hyperexcitability appears to be the most likely mechanism (Brown 1994; Li and Francisco 2015). RS hyperexcitability provides unopposed excitatory descending inputs to spinal stretch reflex circuits, resulting in elevated excitability of spinal motor neurons and hyperreflexia. This adaptive change can account for most clinical findings, for example, exaggerated stretch reflex, velocity-dependent resistance to stretch, muscle overactivity, or spontaneous firings of motor units. Such muscle overactivity in a joint position at a shortened muscle length facilitates limb immobilization, development of muscle and tendon contractures, and accumulation of extracellular matrix deposits (Stecco et al. 2014; Raghavan et al. 2016). Muscle fiber shortening and fibrosis secondary to limb immobilization increase mechanical muscle stiffness. Hyaluronan is the primary component in the extracellular matrix (Fraser et al. 1997). Accumulation and crowding of hyaluronan decrease lubrication between different layers of collagen and muscle fibers, thus perceived as increased stiffness (Stecco et al. 2013). Though not adequately distinguished in clinical (Vattanasilp et al. 2000) or laboratory examinations (Malhotra et al. 2009), these components collectively contribute to increased resistance or spastic hypertonia.

Understanding the different mechanisms of weakness and spasticity and the various components of spastic hypertonia provides a useful theoretical framework to understand the clinical presentations and problems related to spasticity and, subsequently, to develop treatment plans for an effective motor rehabilitation program. Clinical presentations of spasticity vary widely across individuals within and across patient populations. Common postural patterns, including elbow flexion, finger flexion, and equinovarus, are shown in Fig. 1. It is of clinical significance to understand that abnormal postures are almost always manifestations of imbalance of weakness and hypertonia. For example, a flexed elbow posture is not necessarily due to flexor muscle group hypertonia solely, but may be a combination of hypertonic flexors and weak extensors; or it could also be that both flexor and extensor muscle groups are both hypertonic, but the former predominates. It is important to point out

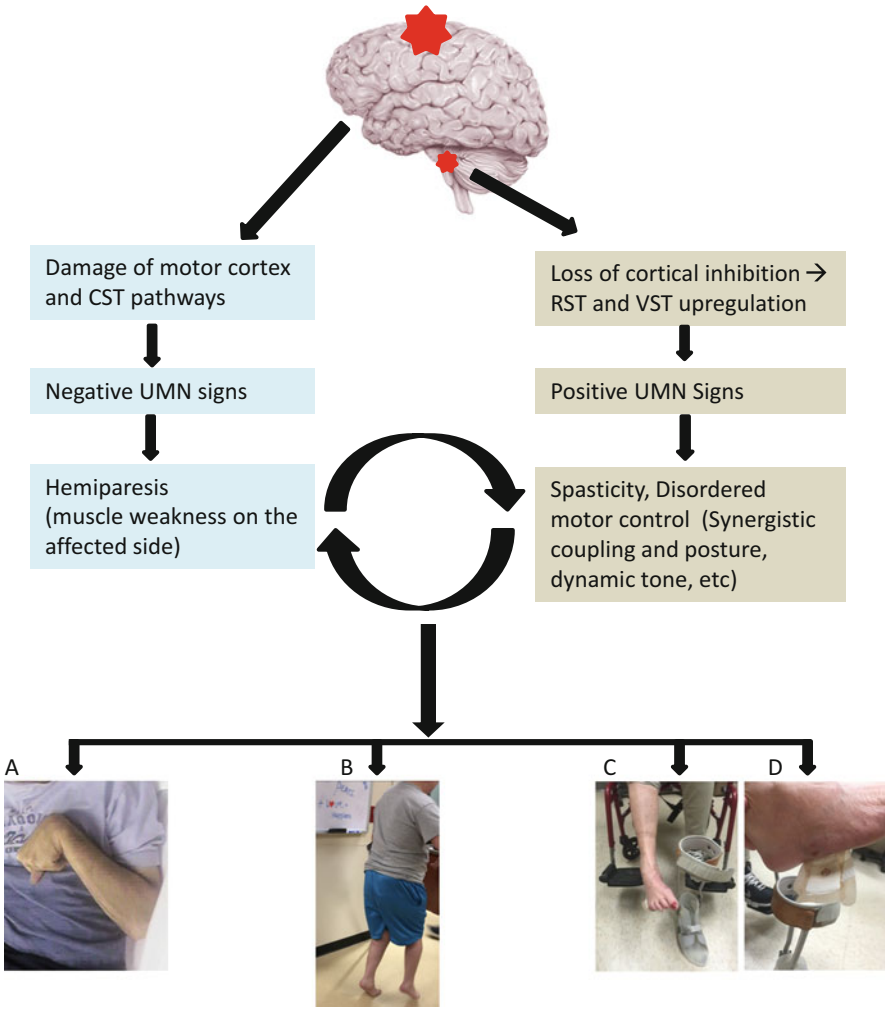

Fig. 1 Pathophysiology of spasticity and its relations to clinical problems. *UMN* upper motor neuron, *CST* corticospinal tract, *RST* reticulospinal tract, *VST* vestibulospinal tract, *MN* motor neuron (**a**) Abnormal posture leading to difficulty with hygiene and dressing; (**b**) Abnormal gait; (**c**) Spastic equinovarus; (**d**) Pressure sore

that clinical problems of spasticity are not the abnormal joint postures caused by spasticity; instead, consequences of abnormal joint postures are usually the problems. As shown in Fig. 1, difficulty to clean the clenched fist and armpit is more problematic than the non-movable clenched fist and shoulder joint, because it may lead to skin maceration and infection. Similarly, the problem of a spastic equinovarus is mainly manifested by the pressure sore developed during constant abnormal pressure during walking. Impaired motor control of spastic muscle is another example of clinical problems associated with spasticity. Sustained activation

of spastic calf muscles during weight-bearing can cause spastic foot drop and abnormal gait pattern (Fig. 1). This theoretical framework can also guide the development of treatment plans. These are detailed in the management section.

3 Goal-Setting and Goal-Oriented Clinical Assessment

It is clear that spasticity is only one component of the clinical problems, as mentioned above. The problems are usually associated with consequences of spasticity or disordered motor control that a limb could not be moved, or the resultant functional limitations, such as the inability to release a grasped object or difficulty with walking due to an in-turned foot. Spastic muscles should be treated only if they are causing or predisposing to other problems. However, it is not uncommon for patients to desire goals of regaining normal function, but since this is usually not achievable, a discussion regarding goal-setting prior to initiating treatment can help manage expectations of treatment outcomes.

Patient-centered goal-setting should be the key driver of management decision-making. Treatment goals should be mutually agreed upon by the patient (or caregiver) and clinician. All factors should be considered, including findings from focused medical history, functional history, the patient's realistic expectations, inputs from care-provider(s) and therapists, and social support system. For example, a medical cause of a transient increase in the severity of spasticity, such as urinary tract infection or pressure sores, should be considered and treated prior to setting the treatment goal. It is therefore important to obtain a thorough, yet focused, medical and functional history to guide the examination and to formulate treatment goals and plans. A systematic approach to history-taking and clinical assessment of spasticity is proposed in Tables 1 and 2. It can be modified for different clinical scenarios.

Spasticity of individual muscles and muscle groups is often assessed by clinical scales. The commonly used scales include the Ashworth scale (AS), the modified Ashworth scale (MAS), and the Tardieu scale (Tables 3 and 4). The Tardieu scale has advantages over the MAS because it not only quantifies the muscles' reaction to stretch, but it controls for the velocity of the stretch and measures the angle at which the catch, or clonus, occurs. However, neither scale has shown to be more reliable than the other. In addition, a limitation of both Tardieu and AS/MAS scales is the fact that they are performed at rest, whereas spasticity may be bothersome during active function when the person is upright and attempting to move or perform an activity. Thus these clinical assessments do not correspond with the treatment goal.

Quantitative measures, such as biomechanical and electrophysiological tests, are desirable because of their inherent objectivity and reliability. Unfortunately, many of the devices are not available to a typical clinician, or the tests are too time-consuming. On the other hand, clinical problems are the consequences associated with spasticity, rather than the spasticity itself in most situations. Clinical scales are often sufficient to guide the treatment.

Table 1 Some important medical and functional history in spasticity assessment

Medical history
• Is there any new medical condition? (e.g., urinary tract infection, other infections)
• What are the current medications? (e.g., any spasmolytic agents? And dose?)
• Is there any change of medications? (e.g., addition of neurostimulants)
• Was there a recent increase in tightness (that may warrant further diagnostic testing to rule out a new neurologic or medical problem)?
• What treatments for muscle tightness have been tried previously and their outcome?
Functional history
• Is the limb tight all the time or only at certain times?
• Does a particular position or movement trigger tightness?
• Is the tightness related to spasms?
• Does the tightness cause pain?
• Have there been episodes of skin compromise due to tightness or spasm?
• Does the tightness result in difficulty with cleaning?
• Does the tightness result in difficulty donning splints?
• Does the tightness limit the ability to move limbs, reach for objects, and use the hands?
• Does the tightness of the lower limbs result in problems with transferring from one surface to another or with walking?

Table 2 Practical clinical examination sequence

Tasks	What to look for	What can be gleaned
Observation	Observe limb posture at rest and how they change with position	Abnormal posture at rest – sustained muscle contraction (dystonia), contracture, pressure sore, wound (that would worsen spasticity)
Voluntary and functional activities[a]	How limbs move and how much active range is available Gait characteristics and associated upper limb and trunk postural abnormalities	Functional strength, coordination, spastic co-contraction, contractures, presence of other movement disorders, synkinesis, or associated reactions Position-dependent postural changes – dynamic tone Pain and discomfort during voluntary and functional movements
Passive (MAS, AS, Tardieu)	Passive range of motion, strength, muscle tone, velocity-dependent "angle of catch," clonus	Spasticity Rigidity Contracture Clonus Pain and discomfort during passive stretch

[a]Voluntary movements, such as sit to stand, transfer, ambulation, and other functional activities

Table 3 Modified Ashworth scale

0	No increase in muscle tone
1	Slight increase in tone, manifested by a catch and release at the end of range of motion (ROM)
1+	Slight increase in tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM (catch in the first half of ROM)
2	Marked increase in tone through most of the ROM, still easily moved
3	Considerable increase in tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Table 4 Tardieu scale

Quality of muscle reaction
0. No resistance
1. Slight resistance
2. Catch followed by a release
3. Fatigable clonus (<10 s)
4. Continuous clonus (>10 s)
Angle of muscle reaction at different velocities of stretch
V1. As slow as possible
V2. Speed of limb falling under gravity
V3. As fast as possible

4 Botulinum Toxin (BoNT) Therapy for Spasticity Management and Related Clinical Issues

There are a number of treatment options for management of spasticity, including physical modalities; oral medications; chemodenervation with botulinum toxins (BoNT), phenol, or alcohol; intrathecal baclofen therapy; and surgical interventions. There are different approaches to utilize these treatment options, e.g., the sequential approach from the least invasive treatment to surgical procedure and combined therapy with both "invasive" and "noninvasive" treatments. Selection of treatment options is discussed in more detail elsewhere (Francisco and Li 2015).

Nevertheless, chemodenervation with BoNT has become a widely used spasticity treatment. It is preferred for the management of focal spasticity or when the treatment plan targets a particular muscle (Simpson et al. 2016). Botulinum toxin exerts its effect through inhibition of acetylcholine release at the neuromuscular junction via a complex process (see other chapters for details) (Wheeler and Smith 2013; Jankovic 2017; Pirazzini et al. 2017). Currently, serotypes A and B of *Clostridium botulinum* are utilized clinically: *abobotulinumtoxinA*, *incobotulinumtoxinA*, *onabotulinumtoxinA*, and *rimabotulinumtoxinB*. They all inhibit acetylcholine release and the muscle paralysis they produce is reversible. The clinical effects of BoNT do not manifest until several days following an injection. The clinical effects last about 3 months, and recurrence of spasticity is likely due to functional repair of the neuromuscular junctions previously paralyzed by the toxin (de Paiva et al. 1999). Usually, patients require repeated BoNT

injections every 3–4 months (Moeini-Naghani et al. 2016; Simpson et al. 2016). However, majority survey of treating physicians and patients found that a majority prefer more frequent injections to achieve better clinical outcome (Bensmail et al. 2014). A new injectable BoNT, daxibotulinumtoxinA (an investigational BoNT, RT002), may offer a more prolonged duration of treatment effect (Jankovic et al. 2018). Though still under investigation (Fonfria et al. 2018; Webb 2018), engineered BoNT appears able to enhance receptor binding and thus increase the efficacy of BoNT (Tao et al. 2017). Advantages of BoNT treatment over oral medications are target specificity and a more favorable adverse event profile. Drowsiness and sedation are practically nonexistent with BoNT treatment.

Over three decades, overwhelming evidence demonstrates that BoNT therapy results in significant improvement at the body function and structure level (Bakheit et al. 2000; Burridge et al. 2005; Rosales and Chua-Yap 2008; Simpson et al. 2008; Wissel et al. 2009; Bensmail et al. 2010; Sheean et al. 2010; Shaw et al. 2011; Rosales et al. 2012; Lampire et al. 2013; Holman Barden et al. 2014; Tenniglo et al. 2014). In a recent meta-analysis study that included 40 trials (Andringa et al. 2019), the authors reported robust evidence of BoNT on reducing resistance to passive movement and on self-care, as measured with the (modified) Ashworth scale, and improving self-care ability for the affected side after intervention and at follow-up. Similarly, evidence of the absence of the effect on the "arm-hand capacity" at follow-up was also robust. BoNT significantly reduced "involuntary movements," "spasticity-related pain," and "carer burden" and improved "passive range of motion," while no evidence was found for "arm and hand use" after the intervention.

The main clinical issue is how to achieve the best outcome with BoNT therapy. The relevant issues are (1) medication related (dosing, dilution, molecular manipulation, and immunoresistance), (2) injection related (injection guidance and motor innervation zone), (3) use of adjunct therapy, (4) relation to motor recovery (therapeutic weakness and central mechanisms), and (5) alterative treatment options.

Dosing Clinical experience, regulatory and insurance coverage restrictions, and manufacturers' recommendations based on a few studies largely dictate the choice of doses of the various botulinum toxins. There are a handful of dose-ranging studies that define dose-related therapeutic and adverse effects in spasticity (Bhakta et al. 1996; Simpson et al. 1996, 2016; Hyman et al. 2000; Baker et al. 2002; Childers et al. 2004; Gracies et al. 2014). Dosages that are used in current practice recommended by consensus statements (Wissel et al. 2009) are higher than doses used in published randomized controlled studies. The use of escalating doses of botulinum toxins was becoming a common practice until safety concerns were raised and fueled by mandates from the US Food and Drug Administration (FDA). Responding to reports suggestive of systemic toxicity of botulinum toxins, in 2009 the FDA required new label warnings and a risk mitigation strategy that requires clinicians to discuss the risks and provide written material that details the warnings. The current experience of many clinicians is that using dosages of inco- and onabotulinumtoxinA as high as 600–800 units (U) is effective and safe (Santamato et al. 2013; Wissel et al. 2013). Two comprehensive reviews concluded that higher

doses of botulinum toxin type A appeared to be efficacious in reducing spasticity of the upper and lower limbs after stroke, with minimal adverse effects (Santamato et al. 2015; Baricich et al. 2018). Recently, Wissel et al. (2017) reported on the safety and efficacy of escalating doses of incobotulinumtoxinA up to 800 units. The resistance to passive movement scale improved significantly. The proportion of subjects achieving at least three of four pre-identified treatment goals increased with higher doses of the toxin. No neutralizing antibody was detected.

Dilution It is believed that increasing the volume of botulinum toxin solution injected magnifies its therapeutic effects by facilitating the toxin's ability to reach more motor endplates. This has been demonstrated in animal studies (Shaari and Sanders 1993; Kim et al. 2003) where muscle paralysis and atrophy were greater when a more dilute preparation, i.e., higher volume relative to dose, or lower concentration, of botulinum toxin is injected. Human studies are equivocal in demonstrating superiority of higher volumes of botulinum toxin injections (Francisco 2004; Lee et al. 2004) largely due to methodological limitations of studies although some investigation have found that high-volume or endplate-targeted botulinum toxin injections result in more profound neuromuscular blockade and spasticity and co-contraction reduction, as compared to low-volume, non-endplate-targeted injections (Gracies et al. 2009). As much as high-volume injections appear attractive, it may be a double-edged sword in that it may facilitate distant spread of the toxin. Cases have been reported wherein patients with poststroke spasticity who receive large dilution volumes in proximal upper limb muscles developed transient weakness in the non-injected contralateral upper limb. Based on electrophysiologic abnormalities documented following the injection, weakness was attributed to neuromuscular blockade.

Techniques to Enhance BoNT Effectiveness There is a lot of interest in techniques to enhance the clinical effects of botulinum toxin, without concomitantly increasing the risk for adverse events. According to the mechanism of action of BoNT – blockade of acetylcholine release at the neuromuscular junction, different techniques have been tried. Injections at multiple sites within a muscle and using a higher-volume/more dilute toxin solution (already discussed above) are regarded as ways to reach more neuromuscular junctions, than to increase effectiveness. Other techniques used to attempt enhancement of toxin effectiveness include guided injection by listening to EMG activity, motor point identification through electrical stimulation (ES), or visualizing target sites by sonography. The superiority of one guidance technique over another is yet to be established, but consistently studies have demonstrated that EMG, ES, or sonography is better than anatomic localization through muscle palpation (Schnitzler et al. 2012; Picelli et al. 2014a, b, c; Ploumis et al. 2014).

A novel neuroengineering technique can provide information of accurate localization of neuromuscular junctions of a muscle (Barbero et al. 2012). Using surface EMG recording with a high-density EMG electrode, neuromuscular junctions can be determined from visual inspection or analysis of surface EMG signals. This surface

projection is called innervation zone (IZ). In healthy subjects, it has been shown that the effect of BoNT decreases by 46% if BoNT is injected by 1 cm away from the innervation zone (Lapatki et al. 2011). Due to secondary and adaptive changes, IZ location changes in the spastic muscles after stroke. The difference in IZ locations between spastic biceps muscle and the contralateral biceps muscles was up to 3 cm (Bhadane et al. 2016). Through advanced computational algorithms, the information of the depth of IZ locations within the biceps muscles is obtained and validated, i.e., IZ location in three-dimensional space within a muscle (Zhang et al. 2017, 2019). Comparisons of clinical outcomes of BoNT therapy between IZ-guided injection and conventional methods are ongoing in our lab. As expected, our preliminary data showed better reduction in spasticity after IZ-guided injection.

Adjunctive Therapies to Enhance the Effect of BoNT Therapy When used alone or in combination of BoNT therapy, physical modalities have been shown to be effective in reducing spasticity and increasing range of motion. Splinting and casting are often used in the acute setting for sustained stretching to prevent contracture and reduce spasticity (Booth et al. 1983; Preissner 2002; Mortenson and Eng 2003; Pohl et al. 2003; Bovend'Eerdt et al. 2008). Casting alone seems sufficient to prevent contracture and reduce spasticity if the intervention is initiated early after severe brain injury. However, a systematic review on the use of upper extremity casting found high variability in casting protocols which indicates no consensus in technique (Lannin et al. 2007). Casting can enhance the effect of onabotulinumtoxinA (Farina et al. 2008), as prolonged stretching of spastic muscles after BoNT injections affords long-lasting therapeutic benefit. Another promising technique to magnify the clinical effect of BoNT therapy is pairing it with superficial electrical stimulation, which influences activity of synaptobrevin-2 receptors that facilitate neuronal binding and subsequent uptake of BoNT (Hesse et al. 1998; Bayram et al. 2006; Mayer et al. 2008; Wilkenfeld 2013). More recently, extracorporeal shockwave therapy (ESWT) has been shown to have a greater magnitude of BoNT enhancement than electrical stimulation, most likely through modulation of muscle rheology and neurotransmission (Santamato et al. 2013; Wilkenfeld 2013). For a more in-depth discussion of this topic, Mills et al. (2016) conducted an excellent systematic review of how adjunct therapies improve outcomes of botulinum toxin injections for spasticity.

Early Treatment: When to Start BoNT Therapy? There is no standard in how early BoNT can be safely and effectively administered. A few studies reported that treatment as early as 3–6 months of disease onset effectively manages muscle hypertonia and decreases risk of later complications, such as contracture development (Hesse et al. 2012; Fietzek et al. 2014). Results of an exploratory, double-blind, randomized, placebo-controlled trial (Rosales et al. 2018) using abobotulinumtoxinA 500 U in subjects with upper limb spasticity within 2 to 12 weeks poststroke suggested that early treatment significantly delayed time to reach reinjection criteria when compared with placebo.

Repeated Injections: Are Repeated Injections "Safe"? In clinical practice many patients receive multiple injections over a period of many years, sometimes decades, while the long-term effects are not systematically documented. The fact that patients continue to receive BoNT therapy over a long period of time implies that the patients continue to benefit from it. Most studies involving the use of botulinum toxin for spasticity involve only a few cycles of injection. A rare few have reported safety and sustained efficacy up to five injection cycles over a few years (Lagalla et al. 2000; Gordon et al. 2004; Elovic et al. 2008; Santamato et al. 2017). Although the few studies claimed that repeated injections were safe, concerns remain about the long-term effect of BoNT on muscles. An animal study concluded that the contractile properties of target and nontarget muscles did not fully recover within 6 months of BoNT injections (Fortuna et al. 2013). The same investigators also found that following repeated BoNT injections muscle atrophy sets in and contractile material is replaced by fat (Fortuna et al. 2011). Recognition of BoNT's effects on muscle length and force (Turkoglu et al. 2014) is also emerging, although how this translates clinically is still unclear. These concerning findings need to be investigated further in clinical studies emphasizing muscle changes in recovery after BoNT injections.

Poor Responses to BoNT Therapy: What Are the Reasons? The effectiveness of BoNT therapy in spasticity reduction is well documented, as discussed above. However, the response varies from person to person. Poor response is defined as the treatment goals are not met. There are many potential reasons for poor responses to BoNT therapy in spasticity management (Table 5). One of the most common reasons is unrealistic expectations from patients and family members and/or caregivers. It is important to set the treatment goals prior to BoNT therapy, and the goals need to be agreed upon between the patient and the treating physician. What needs to bear in mind is that not all increased resistance (hypertonia) is caused by spasticity, as discussed in the Pathophysiology and the Clinical Presentations. Adaptive muscular changes are likely to occur, such as hyaluronan accumulation, muscle fiber shortening, and fibrosis. Hypertonia caused by these changes is not expected to respond to BoNT therapy. On the other hand, alternative treatment options should be used. Hyaluronidase is an enzyme that hydrolyzes hyaluronan. It is reported that hypertonia was significantly reduced after hyaluronidase injection (Raghavan et al. 2016).

Table 5 Potential reasons for poor outcome of botulinum toxin therapy

Patient-related	Injector-related	Drug-related
Unrealistic expectations Disease conditions Concurrent medications that interact with spasmolytic drugs or alter muscle tone Immunoresistance Secondary muscle changes, fibrosis, etc.	Incorrect diagnosis Incorrect muscle selection Improper injection technique (far away from the neuromuscular junction)	Incorrect dose (over- or underdose) Incorrect preparation Inactive medication

Immunoresistance is a potential factor that causes suboptimal or no responses to BoNT therapy. Bioassay of neutralizing antibodies (NABs) to BoNT is considered the gold standard in confirming immunoresistance. Based on early reports in the cervical dystonia population, high doses and frequent injections of BoNT were identified as risk factors for immunoresistance (Zuber et al. 1993; Greene et al. 1994).This also provided support for the practice of allowing no less than 90 days in between exposures to BoNT. A much higher incidence of antibody formation has been associated with cervical dystonia than in spasticity (Naumann et al. 2010). There is a growing interest in incobotulinumtoxinA, which is free of excipient proteins and, as such, may have a lower propensity to induce an immunogenic response relative to the other botulinum toxin preparations with complexing proteins (Albrecht et al. 2019). A meta-analysis of 16 clinical trials involving a total of 3,006 subjects with various diagnoses found that neutralizing antibodies determined by mouse protection assay appeared in 1.28% of cervical dystonia, as opposed to only 0.32% poststroke subjects. In another pooled analysis involving three 12- to 42-week clinical poststroke spasticity studies, the formation of neutralizing antibodies was found to be 0.5% (1/191 subjects) (Yablon et al. 2007). However, there are heterogeneous reports. In children with cerebral palsy, high neutralizing antibody (NAB) frequencies of up to 30% have been described (Herrmann et al. 2004). The most significant risk factors for antibody formation were frequent treatment and high dose per treatment in this study. In a more recent cohort of patients with different neurological impairments, 83 of 596 patients (13.9%) had measureable NAB (Albrecht et al. 2019). The probability of developing antibodies increased with repeated treatment and was influenced by the BoNT/A formulation. The NAB rates were similar for aboBoNT/A and ona-BoNT/A (6% and 7%, respectively), while no NABs were observed in patients treated exclusively with inco-BoNT/A. The difference in NAB rates is likely related to the amount of 150 kDa BoNT/A neurotoxin. It was found that, at current FDA-approved doses, abobotulinumtoxinA contains greater amounts of active neurotoxin as compared to other BoNT/A products (Field et al. 2018). Disease entity and treatment duration had no additional influence (Albrecht et al. 2019). In the same study (Albrecht et al. 2019), those patients with positive NABs still responded to BoNT therapy (at least partially), while NAB was positive in only 57% (20 out of 35) in patients with spasticity who failed BoNT therapy. Overall, the prevalence of NAB has dropped from 10% in the past (Jankovic et al. 2003) to the current level about 1% (Mathevon et al. 2019), with no NABs in patients treated with inco-BoNT/A (Albrecht et al. 2019). Therefore, it is important to note that it is extremely rare that NAB is the cause of non-responders (Jankovic 2017; Mathevon et al. 2019).

Recovery of Motor Function: Can BoNT Therapy Help Recover Motor Function in a Subgroup of Patients? The evidence is robust for the effect of BoNT therapy in spasticity, while it is also robust that BoNT therapy does not improve voluntary movement (Andringa et al. 2019). However, there are unusual cases when the outcome of BoNT injections surpasses this expectation and results in an increase in functional abilities of the hand in chronic stroke survivors (Fridman et al. 2010;

Chang et al. 2012; Mas et al. 2017). In a case study (Chang et al. 2012), the patient was a 53-year-old female, who sustained a hemorrhagic right middle cerebral artery stroke 3 years earlier. She had finger flexor spasticity and residual weak finger/wrist extension. She received 50 units of onabotulinumtoxinA injection to each of the left flexor digitorum superficialis and flexor digitorum profundus, respectively. As expected, BoNT injection led to weakness and spasticity reduction in the spastic finger flexors. However, she was able to open her hand faster due to improved grip release time. This was accompanied by shortened finger flexor EMG activity during hand and finger opening. Similarly, another chronic stroke survivor regained the ability to open the hand 4 years poststroke after several BoNT injections to finger flexors (Mas et al. 2017). In these cases, natural motor recovery is not likely after 3 to 4 years after stroke. Regardless of underlying mechanisms, these reports suggest that late motor recovery is possible in selected chronic patients when motor recovery is presumed plateaued.

Advancement in understanding the pathophysiology of spasticity helps understand the phenomenon of late motor recovery after BoNT injections. As illustrated in Fig. 1, spasticity and weakness are mediated by different mechanisms secondary to neural plasticity (Li 2017). When finger flexor spasticity is addressed by BoNT injections, with concomitant reduction in spastic co-contraction in finger flexors during finger extension attempts (Chang et al. 2012), weak finger extensors became functional, and motor function of the hand improved. In this regard, weakness produced by BoNT injection is therapeutic, i.e., therapeutic weakness (Francisco and Li 2015). It follows that interventions to strengthen the finger extensors after BoNT injections to the spastic finger flexors are expected to better improve motor recovery. The expected results were confirmed in a recent study (Lee et al. 2018).

Central Effects: Does the BoNT Effect Go Beyond the Injected Muscles? As described earlier, the therapeutic effects of BoNT therapy on spasticity reduction is widely accepted to be realized via blockade of acetylcholine release presynaptically at neuromuscular junctions of the targeted muscles. Neuromuscular blockade affects both extrafusal and intrafusal muscle fibers (Filippi et al. 1993; Rosales et al. 1996). It is estimated that BoNT injection results in a decrease in activity of intrafusal muscle fibers, i.e., afferent input by 33%. Such decrease was found to be greatest at 2 weeks, and tapered off at 12 weeks postinjection, and correlated with spasticity reduction (Phadke et al. 2013). BoNT-related blockade at intrafusal fibers decreases spindle inflow to spinal stretch reflex circuits, thus contributing to spasticity reduction. Furthermore, decreased afferent inputs via intrafusal blockade can further alter spinal motor neuron excitability and sensorimotor integration. Trompetto et al. reported that suppression of tonic vibration reflex was still observed at 7 months after BoNT injection when muscle strength and the magnitude of maximal M-wave have fully recovered (Trompetto et al. 2006). In another study, recurrent inhibition from soleus motor axons to motor neurons supplying the quadriceps muscle was suppressed after BoNT injection in the soleus muscle (Marchand-Pauvert et al. 2013). This suppression was considered to be induced by BoNT through axonal transport and blockade of the cholinergic synapses of

Renshaw cells. Accumulated evidence from animal and human studies have shown that intramuscularly injected BoNT could reach further to brainstem and cortical levels indirectly through hematogenic spread, retrograde transport of BoNT, and plastic reorganization of the central nervous system due to altered afferent inputs (see reviews Mas et al. 2017; Caleo and Restani 2018; Weise et al. 2019). Collectively, substantial evidence demonstrates that intramuscularly injected BoNT is able to reach and modulate excitability of motor neurons at the spinal and supraspinal levels.

Alternative Treatment Options: When Not to Use BoNT Therapy for Spasticity Management? BoNT therapy is the preferred treatment option and is widely used for spasticity management. However, there are a number of other treatment options. To know when not to use BoNT therapy for spasticity management is also very important, since different treatment options have their advantages and indications as well, and BoNT therapy also has potential adverse effects, even if rare. For example, how many BoNT injections need to be done to address a spastic-dystonic "clenched fist" before surgical release of the finger and thumb flexor tendons should be entertained? How many times should a person with severe spastic paraplegia receive BoNT injections before intrathecal baclofen therapy is considered? The economic impact of these clinical decisions will also need to be weighed to better appreciate the cost-effectiveness of spasticity interventions. An alternative, such as hyaluronidase, may be considered to address different components of spastic hypertonia when there is suboptimal response to BoNT injections (Raghavan et al. 2016). Phenol neurolysis is likely to be a better choice to address moderate to severe spasticity for an inpatient where its immediate effects on spasticity reduction would be highly appreciated (Karri et al. 2017). Other emerging adjunctive therapies, such as noninvasive brain (Kumru et al. 2010; Wu et al. 2013; Barros Galvao et al. 2014; Gunduz et al. 2014), spinal (Pinter et al. 2000), and transcutaneous nerve (Hofstoetter et al. 2014; Oo 2014) stimulation, may be considered to enhance the effect of BoNT therapy.

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