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REVIEW

Treatment with botulinum toxin: An update

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Abstract

Botulinum neurotoxin (BoNT) is a potent toxin produced by the anaerobic bacterium clostridium botulinum. It causes flaccid, long-lasting, local and reversible paralysis. In addition, BoNT inhibits the secretion of the exocrine glands and could have properties in the control of pain. Thus, BoNT is useful in the treatment of many neuromuscular conditions where an increase of muscle tone is associated with the pathogenic mechanism. Furthermore, BoNT is recommended in the treatment of some hypersecretion disorders of the exocrine gland and could play a role in the treatment of migraine and other chronic pain conditions. In the BoNT therapy adverse effects are usually mild and reversible. However, repeated injections of BoNT can lead to the development of neutralizing antibodies that can subsequently inhibit the biological activity of the toxin. In this sense, many factors can influence the immunogenicity of the BoNT, such as product-related factors, the dose of BoNT used, the frequency of injection and the previous exposure to the toxin. In this review, we are going to discuss the current clinical applications of BoNT with a special focus on evidence, doses, injection technique and adverse effects for those applications more frequently used in neurology, namely spasticity, blepharospasm, hemifacial spasm, cervical dystonia and other focal dystonias, as well as chronic migraine, tremor, sialorrhea, facial palsy, neurogenic bladder and many other neurological condition.

Key words: Botulinum toxin; Dystonia; Spasticity; Headache; Migraine; Pain; Tremor; Sialorrhea; Facial palsy; Neurogenic bladder

Core tip: In this review we are going to discuss evidence, doses, injection techniques and adverse effects of the botulinum neurotoxin therapy for those indications more frequently used in neurology.

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INTRODUCTION

Botulinum neurotoxin (BoNT) is a potent toxin produced by the anaerobic bacterium clostridium botulinum[1]. It causes flaccid, long-lasting and reversible paralysis by inhibiting exocytosis and can thus prevent acetylcholine release at the neuromuscular junction[2]. In addition, the effects of local injections of BoNT are usually limited to the applied area[2], although it is possible that BoNT could spread beyond the muscle injected causing adverse effects it is not frequent. Thanks to these attributes, BoNT has been found to be useful in the treatment of many neuromuscular conditions where an increase of muscle tone is associated with the pathogenic mechanism. Furthermore, BoNT could be helpful in the treatment of migraine and other chronic pain conditions. For these indications, the mechanism of action has not been fully elucidated, but could be due to the inhibition of the release of nociceptive inflammatory mediators, such as calcitonin gene-related peptide, glutamate and substance *P* from the peripheral termini of nociceptors. Inhibiting the release of these neurotransmitters prevents neurogenic inflammation and subsequent peripheral sensitization;

as a result, peripheral pain signals to the central nervous system are reduced. Thus, BoNT might indirectly block central sensitization for pain[3]. Finally, BoNT inhibits the release of presynaptic acetylcholine at the neurosecretory junctions[4]; therefore, it could play a role in the treatment of hypersecretion disorders of the exocrine glands.

BoNT is a protein complex consisting of a 150-kDa core neurotoxin and a number of associated non-toxic accessory proteins (NAPs) whose function is to stabilize and protect the core neurotoxin from low pH, enzymatic degradation an changes in temperature[5]. There are seven serotypes of BoNTs (termed A-G)[2], but only serotypes A (BoNT-A) and B (BoNT-B) are commercially available. Of these serotypes, the four most widely used formulations in clinical practice are three of the BoNT-A serotypes, named OnabotulinumtoxinA (A/Ona, Botox, Allergan, Irvine, CA, United States), AbobotulinumtoxinA (A/Abo, Dysport, Ipsen Biopharm, Wrexham, UK) and IncobotulinumtoxinA (A/Inco, Xeomin, Merz Pharmaceuticals, Frankfurt, Germany), and one BoNT-B serotype named RimabotulinumtoxinB (B/Rima, NeuroBloc/Myobloc, Eisai, Tokyo, Japan).

BoNT doses are expressed as mouse units for adults and as mouse units per kg body weight (units/kg bw) for children[6,7]. One mouse unit is defined as the amount that kills 50% of a group of mice when injected intraperitoneally[6]. Note that all BoNT formulations are distinct concerning their molecular structure and their manufacturing process[7]. Indeed, the methods used for determining biological activity are also different[7]. These pharmacological differences have significant implications for clinical use. Thus, individual dosages should be calculated independently for each BoNT formulation and therefore, fixed dose-conversion factors should not be used[7].

Repeated injections of BoNT can lead to the development of neutralizing antibodies that can subsequently inhibit the biological activity of the toxin[5]. Many factors can influence the immunogenicity of the BoNT. First, product-related factors, such as the manufacturing and storage processes, the toxin source and the antigenic protein load of each formulation, together with the excipients and the presence of NAPs can influence the immunogenicity[5]; Second, BoNT immunogenicity may be related to the dose that is injected. Indeed, the development of neutralizing antibodies is correlated to the increasingly cumulative doses[5]; Third, BoNT immunogenicity may be associated with the frequency of injection; injection intervals shorter than 2 mo may increase the risk for neutralizing antibody formation[5]; Finally, previous exposure to or vaccinations against BoNT may also affect the immunogenicity[5]. As a result, A/Inco, a new BoNT-A developed free from NAPs, has shown low rates of neutralizing antibodies and could have an improved immunogenicity profile[5,8].

Our aim is to review the current clinical applications of BoNT with a special focus on those applications more frequently used in neurology.

DATA SEARCH

The Cochrane Library and Medline databases were systematically searched with special focus in the last ten years. The search terms were "botulinum toxin" or "onabotulinumtoxina" or "incobotulinumtoxina" or "abobotulinumtoxina" or "rimabotulinumtoxinb" and "mechanism of action" or "targeting" or "neutralizing antibodies" or "dystonia" or "blepharospasm" or "hemifacial spasm" or "cervical dystonia" or "occupational dystonia" or "writer"s cramp" or "spasmodic dysphonia" or "oromandibular dystonia" or "spasticity" or "headache" or "myofascial pain syndrome" or "facial pain" or "neuropathic pain" or "migraine" or "tensional headache" or "cervicogenic headache" or "cluster headache" or "piriformis syndrome" or "temporomandibular dysfunction" or "trigeminal neuralgia" or "postherpetic neuralgia" or "sialorrhea" or "drooling" or "tremor" or "facial palsy" or "neurogenic detrusor overactivity" or "detrusor sphinter dyssinergia" or "tics" or "brachial plexus injury" or "stuttering" or "painful leg and moving toes" or "Parkinson´s disease" or "multiple sclerosis". Indeed, further references were obtained through their bibliographies. Finally, between all the references selected, one hundred and eighty five were considered relevant for the purpose of this review.

DYSTONIAS

BoNT therapy is often the treatment of choice for many focal or segmental dystonias. Blepharospasm, hemifacial spasm and cervical dystonia are those with stronger evidence of efficacy, although it could also be helpful in occupational dystonias, spasmodic dysphonia and other dystonias.

In the 1980's, blepharospasm was one of the first indications for BoNT treatment. Years of clinical use and many studies have subsequently shown the efficacy of BoNT in the treatment of blepharospasm[9-16]. However, evidence-based conclusions are variable between the different commercially available formulations due to the lack of well-designed and controlled trials (level A of recommendation for A/Ona and A/Inco, level B for A/Abo and level U for B/Rima)[17].

The treatment technique involves injection into the preseptal portion of the orbicularis oculi at four sites per eye, two in the upper lid (one medially and one laterally) and two in the lower lid (one at the lower lateral canthus and one near the middle of the lower lid)[18]. It is important to avoid injections into the medial two-thirds of the lower eyelid to prevent diplopia due to diffusion of the toxin to the inferior oblique muscle. It is also important to avoid injections close to the levator palpebrae muscle to prevent ptosis and to avoid injections into the central part of the lower lid to decrease entropion[18]. Pretarsal injections could be useful in refractory cases[19]. Electrically induced muscle activation does not increase the effectiveness of BoNT[20].

Table 1 Muscles and doses of botulinum neurotoxin more frequently used in the treatment of dystonias

	Muscles usually injected	Doses of botulinum toxin proposed			
		A/Ona	A/Inco	A/Abo	B/Rima
Blepharospasm	orbicularis oculi	20 u/e	20 u/e	40 u/e	1250 u/e
Hemifacial spasm	orbicularis oculi corrugator frontalis zygomaticus major buccinator depressor anguli oris platysma	10-34 u	10-34 u	53-160 u	1250-9000 u
Cervical dystonia	sternocleidomastoid splenius capitis trapezius levator scapulae scalenii semispinalis	100-300 u	100-300 u	500 u	2500-10000 u
Writer´s cramp	flexor digitorum superficialis flexor digitorum profundus flexor pollicis longus lumbricales extensor pollicis longus extensor indicis extensor digitorum comunis flexor carpi radialis flexor carpi ulnaris Pronator teres	Maximum of 160 u		Maximum of 250 u	
Spasmodic dysphonia	adductor spasmodic dysphonia: thyroarytenoid lateral cricoarytenoid interarytenoid supraglottic muscle complex	Bilateral injection: 0.9 u/vf Unilateral injection: 1.5 u			
	abductor spasmodic dysphonia: posterior cricoarytenoid	3.75 u unilaterally, additionally 0.6-2.5 u in the contralateral muscle			
Oromandibular dystonia	*jaw-closing* OMD: masseter medial pterygoid temporalis	masseter 25-50 u	25-50 u	100 u	2500 u
	jaw-opening OMD: lateral pterygoid submentalis complex	pterigoyds 15-30 u	15-30 u	30-60 u	1000 u
	deviating OMD: contralateral lateral pterygoid	temporalis 20-50 u	20-50 u	80-100 u	
	tongue-protrusion lingual dystonia: intrinsic tongue muscles	Intrinsin tongue muscles 10 u	10 u	30-40 u	

u: Units per session; u/e: Units per eye and per session; u/vf: Units per vocal fold and per session; OMD: Oromandibular dystonia.

The suggested doses of BoNT in the treatment of blepharospasm (per eye) are 20 units of A/Ona and A/Inco, 40 units of A/Abo and 1250 units of B/Rima[18] (Table 1). The duration of action ranges between 2 and 3.5 mo[21]. Adverse effects are transitory and include dry eye, ptosis, lagophthalmos and diplopia[18,21].

The efficacy of the BoNT therapy in hemifacial spasm is strongly supported by several studies[12,22-24] and by long-lasting daily clinical practice. However, due to the lack of well-designed and controlled trials, the available evidence only supports a level B recommendation and only for A/Ona[17].

The injection technique involves several facial muscles depending on the clinical examination[22]; the most frequently treated are the orbicularis oculi, corrugator, frontalis, zygomaticus major, buccinator, depressor anguli oris and platysma[21,25] (Table 1). Doses of BoNT range from 10 to 34 units for A/Ona (aproximately the same for A/Inco[8]), 53 to 160 units for A/Abo and 1250 to 9000 for B/Rima[26] (Table 1). The adverse effects are similar to those found in blepharospasm, including dry eye, ptosis, mild facial weakness, tearing and diplopia and, as in blepharospasm, they are usually transitory[21]. The mean duration of improvement ranged from 2.6 to 4 mo[21].

There is abundant evidence supporting the efficacy of BoNT therapy for cervical dystonia[27-34], which supports a level A of recommendation for A/Ona, A/Inco, A/Abo and B/Rima[17].

The optimal doses of BoNT for cervical dystonia are between 100 to 300 units of A/Ona[34] and A/Inco[8], 500 units of A/Abo[34] and between 2500 to 10000 units of B/Rima[34]. The average duration of maximum improve-

ment is 3.5 mo[35] (Table 1).

Hefter *et al*[36] proposed a useful algorithm to select the muscles to be injected for treating cervical dystonia. Otherwise, selection is usually based on clinical features, such as abnormal posture, muscle palpation, muscle hypertrophy and pain[37]. However, physical examination alone may not be sufficient to detect dystonic muscles in cervical dystonia in some cases. It has been reported that, firstly, 41% of dystonic muscles could be missed and 25% of inactive muscles would be judged dystonic only upon clinical examination[38] and, secondly, different combinations of muscle activated can lead to similar postural abnormalities[39,40]. This report is important because the inadequate selection of muscles may be one cause for non-responsiveness[37]. To resolve this issue, it has been proposed that EMG or PET/CT could be helpful for muscle selection, especially in complex forms of cervical dystonia and in non-responders[37].

The general consensus among most BTX experts is that the targeting of muscles can be based on clinical examination[35]. Nevertheless, extra guidance by EMG, ultrasound and/or CT could be helpful in some cases, such as when the muscles cannot be adequately palpated[35], when the patient develops adverse effects[41], when the patient does not obtain adequate relief of symptoms with conventional approach[35] or when the needle needs to be placed near an important structure[42], such as the internal carotid artery, vertebral artery, pharynx, spinal canal, brachial plexus or the base of the mouth.

The number of muscles injected usually ranges between 2 and 4 with 2 sites of injection per muscle[43]. The adverse effects are usually mild or moderate and transitory. The most frequently reported adverse effects were neck weakness, dysphagia, dry mouth and dysphonia[43].

In the field of writer's cramp and others occupational dystonias, some studies support the efficacy of BoNT treatment[44-48], although the evidence only provides a level B recommendations for A/Ona and A/Abo[17]. However, despite this reported benefit, the withdrawal rate in a long term follow-up was high[49]. This result was most likely due to the wide range of responses, which were frequently mild[50], and the disability due to weakness from injection[51].

With respect to the doses, no more than 160 units of A/Ona and 250 units of A/Abo have been proposed[52] (Table 1). The maximum improvement usually lasts approximately 3 mo[52].

Many muscle groups of the flexor and extensor compartment of the forearm may be involved in the development of the occupational dystonia[52] (Table 1). Thus, the strategy for the BoNT treatment should be the selection of those few dystonic muscles predominantly affected[51]. In this sense, clinical examination with a special focus to distinguish compensatory muscle activity from the real dystonic muscles is usually sufficient[53], although an EMG recording could be helpful in some complex cases[51].

The accuracy of the needle placement into the correct muscle could be poor in the forearm without any guidance[54]. Thus, EMG with or without electrical stimulation and/or ultrasound guidance should be considered in the muscles targeting[53,55].

Weakness is the most common adverse effect; other reported side effects include muscle atrophy, pain, bruising and numbness[52].

BoNT therapy could be helpful for treating the two main types of laryngeal dystonia: adductor or abductor spasmodic dysphonia. However, despite lengthy clinical experience[56], its efficacy is supported by only one controlled trial using A/Ona[57] (level C of recommendation[17]).

The muscles usually involved are the thyroarytenoid for adductor spasmodic dysphonia[56,58] and the posterior cricoarytenoid for abductor spasmodic dysphonia[56,59]. Additionally, in adductor spasmodic dysphonia, further muscles, such as the lateral cricoarytenoid[60], the interarytenoid[61] and the supraglottic muscle complex[62], have been proposed to be involved (Table 1).

Several injection strategies have been reported, but none of them have demonstrated to have a clear benefit over the others. Thus, the selected muscle can be approached either permucosally, through a channeled fiberoptic laryngoscope introduced trans-nasally under video screen visualization[63], or percutaneously, throughout the cricothyroid membrane guided by a laryngoscope[64], EMG[65] and/or by a "point-touch" technique based solely on laryngeal anatomy[66]. Finally, the injection can be uni- or bilateral[67].

There is no consensus on the dose of BoNT to be injected. In adductor spasmodic dysphonia, Blitzer reported an average dose of 0.9 units of A/Ona per vocal fold in the bilateral technique and 1.5 units in the unilateral one[56] (Table 1). In abductor spasmodic dysphonia, the same author suggested that 3.75 units should be injected unilaterally in the more dystonic posterior cricoarytenoid muscle with the option of an additional 0.6 to 2.5 units in the equivalent contralateral muscle[56] (Table 1).

The most common adverse effects reported are breathiness, weak voice, dysphagia and dyspnea[58]. Finally, the mean duration of benefit was over 11 wk[58].

Jaw-deviating, jaw-opening and, especially, jaw-closing oromandibular dystonia[9,68] (OMD) together with tongue-protrusion lingual dystonia[18,53] could also improve with BoNT therapy. The muscles usually injected are the masseter, the medial pterygoid and the temporalis in jaw-closing OMD[18,53], the lateral pterygoid and the submentalis complex in jaw-opening OMD[18,53] and the contralateral lateral pterygoid muscle in deviating OMD[18,53]. Furthermore, in deviating OMD, if it is associated with jaw protrusion, the ipsilateral external pterygoid muscle could additionally be injected[53] (Table 1). Lastly, the intrinsic tongue muscles are usually the target in tongue-protrusion lingual dystonia[18,53]. BoNT doses reported are 25-50/25-50/100/2500 units (A/Ona//A/Inco//A/Abo//B/Rima) for the masseter[18,53], 15-30/15-30/30-60/1000 units (A/Ona//

A/Inco//A/Abo//B/Rima) for the pterygoids[18,53], 20-50/20-50/80-100 units (A/Ona//A/Inco//A/Abo) for the temporalis[18,53] and 10/10/30-40 units (A/Ona//A/Inco//A/Abo) for the intrinsic tongue muscles[18,53] (Table 1). The most frequent side effects reported are dysphagia and dysarthria[68]. The mean duration of response is over 16 wk[68].

Finally, several reports have shown benefits with BoNT in the treatment of other focal dystonias, such as those associated with Parkinson's disease and other atypical parkinsonisms[69], with a special focus in "Off" painful dystonia[70].

SPASTICITY

Many studies have supported the efficacy of the BoNT therapy in the treatment of spasticity in both adults who have acquired brain injury[71-96] and children who have cerebral palsy[97-102], especially to improve muscle tone and passive function in adults and equinus varus deformity in children (level A of recommendation)[103]. Furthermore, other goals, such as the improvement of active function, the treatment of adductor, hamstrings and upper limb spasticity as well as the control of pain and spasms have been suggested[91-95,103,104]. In this sense, the choice of realistic individual treatment goals is very important for the success of the therapy[104-106].

The available formulations whose efficacy in the treatment of spasticity is the most widely supported are A/Ona and A/Abo[7,107]. In both of these formulations, the doses vary between adults and children and should be determined by the individual condition of the patient, the goal of treatment, the amount of spasticity and the muscle volume[104,107]. In this sense, the muscles most frequently injected and their recommended doses of BoNT can be found in several previous reports[84,104,105,108]. In addition, it is important to determine the safe maximum dosages of BoNT to be used without severe adverse events. In this sense, as confidence with BoNT has grown over the years, the maximum dose per session of BoNT recommended for the treatment of spasticity has increased[104]. The reason is that spasticity, especially in children with cerebral palsy, usually involves several muscle groups; therefore, a multi-level treatment strategy beyond the classic focal treatment is needed[104]. Thus, in adults, a maximum dose of 600 units per injection session and 50 units per injection site of A/Ona and a maximum of 1500 units per session and 125 units per site of A/Abo have been proposed[107], although other authors have gone to a maximum of 2000 units of A/Abo per session in the lower limbs, considering 1000 units per lower limb and 500 units per upper limb as an optimal dosage[108]. In children, the recommended safe doses per session are between 1 and 20 (a maximum of 25) units/kg bw for A/Ona and A/Abo[7]; other authors suggest doses up to a maximum of 14.29 units/kg bw for A/Ona and 37.5 units/kg bw for A/Abo[109]. In addition, the maximum doses proposed for children are 400-600 units per session and 10-50 units per site of A/Ona and 500-1000 units per session and 50-250 units per site of A/Abo[7]. In any case, several points should be considered. First, the adverse effects are dose-dependent; therefore, it is recommended to initiate BoNT therapy with doses as low as possible and to increase them according to the patient response[107]. Second, by distributing the total dose over multiple muscles and over multiple injection sites per muscle to avoid the saturation of the injection site, which could spread the toxin to the neighboring structures or into the systemic circulation, significant unwanted side effects can be avoided and are rare[104,105]. Third, it has been suggested that caution be taken for quadriplegic patients who have swallowing and/or respiration problems[104]. Finally, if spasticity is generalized and there are a considerable number of muscle groups involved, other therapies should be considered[105,110]. In this sense, BoNT for spasticity should always be given as part of an integrated and multidisciplinary rehabilitation program where other therapies, such us functional therapies, orthoses, oral medication, intrathecal baclofen and orthopedic surgery are available[7,104,107].

Because BoNT acts by blocking acetylcholine release at the neuromuscular junction, injection into the region of the motor end-plate should increase its efficacy[111]; therefore, it is recommended[107] in those muscles where these motor end-plates are well defined and can be located from external landmarks[112-115].

Clinical examination based on anatomical landmarks is often used for muscle targeting[104]. However, in a recent study, Schnitzler *et al*[116] showed that needle placement based solely in this technique was successful in only the 43% of the injections performed, even for large and superficial muscles. They concluded that muscle palpation and anatomical landmarks are insufficient to ensure the accuracy of muscle injection[116]. Thus, injection guidance with EMG, with or without electrical stimulation, and/or ultrasound should be considered[107]. Another point to consider is the dilution of the BoNT; in this sense, volumes between 1 mL per 100 units and 8 mL per 100 units have been compared and no significant differences in efficacy were found[101,117,118], although dilutions of 8 mL per 100 units could increase adverse effects in children[101]. Finally, local anesthesia, sedation or general anesthesia is recommended, especially in children with cerebral palsy[7].

Patients with spasticity usually require repeated injections of BoNT, although the frequency of sessions should not be more than once every 3 mo[104]. In this sense, sustained activity of the BoNT has been reported with repeated use[107], in addition to long-term benefits, such as a significant improvement in gait pattern and movement capacity[106] together with a delay and reduction of surgical orthopedic procedures[119]. Thus, in children with cerebral palsy, treatment should start as young as possible, when gait patterns and motor function are still flexible[104]. The optimal age often recommended is between 2 and 6 years old[104], although treatment in children under two years of age has also been suggested[109,120].

BoNT therapy for spasticity is safe[106], even in

Table 2 Method of injection of onabotulinumtoxinA for chronic migraine

Muscles injected	Injection sites (both sides)	Doses of A/Ona per muscle (both sides)
Frontalis	4	20 units
Corrugator	2	10 units
Procerus	1 (only one site in the midline of the forehead)	5 units
Temporalis	8	40 units
	Extra 2 optional sites	Extra 10 optional units
Occipitalis	6	30 units
	Extra 2 optional sites	Extra 10 optional units
Trapezius	6	30 units
	Extra 4 optional sites	Extra 20 optional units
Cervical paraspinal muscle group	4	20 units
Total sites range	31-39 total dose range	155-195 units

Adapted from the treatment paradigm based on the PREEMPT clinical program[132]: 155 units of onabotulinumtoxinA (A/Ona) every 12 wk administered to 31 injection sites across 7 specific head and neck muscle areas using a fixed-site, fixed-dose injection paradigm. Furthermore, up to 40 optional units could be administered using a "follow-the-pain" strategy. Each injection site = 0.1 mL = 5 units of A/Ona.

younger patients[109]. Local side effects, such as weakness or hematoma, as well as distant adverse events, such as tiredness or bladder dysfunction, could be present in one-third of injections[7,106], although they are usually mild[106]. The rate of severe adverse events is usually low, even with high doses on BoNT[106]. Nevertheless, a botulism-like syndrome with severe deterioration in respiratory and oromotor function has been reported and should be considered[109,120,121].

HEADACHE, MYOFASCIAL, FACIAL AND NEUROPATHIC PAIN

The role of BoNT in the treatment of headache is controversial[122,123]. Evidence only supports the use of BoNT being helpful in the prophylaxis of chronic migraine[124]. In contrast, the evidence that supports the use of BoNT in other clinical forms of headache, such as episodic migraine, as well as tensional, cervicogenic or cluster headaches, is poor or absent[124-128].

In this sense, several strategies of injection (fixed or "follow the pain") using a wide range of doses have been suggested for different forms of headache without conclusive results[129]. However, only one controlled trial has shown the efficacy of the BoNT therapy in headache[3]. In this study, which was designed for the prophylactic treatment of chronic migraine, patients received 155 units of A/Ona every 12 wk administered to 31 injection sites across 7 specific head and neck muscle areas using a fixed-site, fixed-dose injection paradigm[130] (Table 2). Furthermore, up to 40 optional units could be administered using a "follow-the-pain" strategy[130] (Table 2). The results showed a significant improvement over placebo-treatment in multiple headache symptom dimensions after 24 wk of follow-up, such as headache frequency, headache episodes, the rate of moderate/severe headaches per day and total cumulative hours of headache[3]. Furthermore, patients treated with BoNT used significantly less triptans and had a reduction of headache-related disability[3]. Adverse effects were usually transient, mild to moderate and occurred in fewer than 10% of patients[3]. Adverse effects that were more frequent were muscular weakness, ptosis, muscle tightness and local pain[3]. In summary, the authors concluded that A/Ona is an effective and safe prophylactic treatment for patients who have chronic migraine[3]. Finally, the same cohort was followed an additional 32 wk in an open-label phase. The results showed permanent long-term benefits after repeated injections of BoNT[131].

BoNT therapy has been suggested for the treatment of myofascial pain syndrome occurring at different muscular groups[132]. However, test trials have shown contradictory results; therefore, there are insufficient data to recommend its generalized use[132]. In any case, BoNT could be useful in some subgroups of patients where the evidence is stronger, namely patients with refractory myofascial pain[133], patients with temporomandibular disorders[134,135] and patients with piriformis syndrome[136].

Finally, although some studies have shown the efficacy of BoNT treatment in neuropathic pain syndromes, such as trigeminal neuralgia[137] or postherpetic neuralgia[138], there is insufficient evidence to provide a generalized recommendation for its use[139].

OTHERS INDICATIONS

BoNT could be a treatment option in many other neurological conditions. We are going to discuss the most relevant.

Sialorrhea and drooling are common and disabling manifestations in different neurological diseases, such as amyotrophic lateral sclerosis, Parkinson's disease or cerebral palsy. BoNT has been proposed as a treatment for these hypersalivation disorders because it inhibits the release of presynaptic acetylcholine at the neurosecretory junctions of the salivary glands[140-151]. In this sense, several injection techniques have been reported: first, either the parotid or the submaxillary salivary glands or both were injected[4]. Second, doses of BoNT per session were between 10 to 100 units of A/Ona (2 to 70 units in chil-

dren), between 20 to 450 units of A/Abo (5 to 40 units in children) and 2500 units (1500 to 3000 in children) of B/Rima[4]. Finally, the needle targeting was based on both ultrasound guidance and manual palpation[4].

The reported side effects included dysphagia, dry mouth, chewing difficulty and mandibular luxation[4]. Finally, the duration of therapeutic effects ranged from one and a half to 6 mo[4].

Several studies have shown the effectiveness of A/Ona in treating essential tremor, especially in the hand, head and voice[152-157]. However, the data available are limited[158], the reported benefits were usually modest[17] and the side effects, such as hand weakness, hoarseness and swallowing difficulties were, in some studies, too frequent[154,157]. Thus, BoNT therapy for treating essential tremor should be considered only in medically refractory cases[158].

Facial palsy may lead to unwanted permanent results, namely facial expression asymmetry, synkinesia, myokymia and hyperlacrimation. Several studies have suggested that injections of BoNT into the facial muscles could improve them[159-163].

Additionally, injections of A/Ona into the detrusor muscle or suburethrally *via* either flexible cystoscope under local anesthesia or rigid cystoscope under general anesthesia[164] has been reported as a treatment option in patients with both neurogenic detrusor overactivity and detrusor sphincter dyssynergia with good outcomes and minimal adverse effects[165-168].

In addition, A/Ona could be useful improving motor[169] and phonic[170] components of tics as well as to relieve premonitory sensations associated with them[171]. Furthermore, it could prevent spine disorders related to severe dystonic neck tics[172].

Finally, benefits have been reported when BoNT is used in the treatment of neurological disorders such as obstetric brachial plexus injury[173-177], camptocormia and Pisa syndrome in Parkinson´s disease[178,179], stuttering[180], painful legs and moving toes syndrome[181,182] and myokymia related to multiple sclerosis[183].

CONCLUSION

BoNT is useful and safe for a large number of neurological conditions. In this sense, many new indications are being suggested, not only for disorders where an increased muscle tone is associated with the pathogenic mechanism but also for chronic pain and other maladies. However, in some cases, although significant benefits are shown in daily clinical practice, the level of evidence is low due to the lack of controlled trials. This issue, together with the improvement of targeting techniques in some indications, as well as the problem of neutralizing antibodies, could be interesting goals for future studies.

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