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Towards flexible and tailored botulinum neurotoxin dosing regimens for focal dystonia and spasticity – Insights from recent studies

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ABSTRACT

Botulinum neurotoxin (BoNT) is an effective, well-tolerated, and well-established option for the treatment of dystonic and spastic movement disorders. However, a single approach does not suit all patients, even within one disease indication. The degree of flexibility in treatment protocols is determined by individual product licenses, which often lag behind real-world clinical experience. A number of patient/practitioner surveys conducted recently have highlighted a desire for greater flexibility than that currently approved, both in BoNT doses and in the intervals between consecutive doses. New evidence arising from research conducted during the last few years has opened new avenues for tailoring BoNT treatment to patients' needs. Data suggest that escalating incobotulinumtoxinA doses enables treatment of a greater number of spasticity patterns than current dose limitations allow, without compromising safety or tolerability. Similarly, in patients with cervical dystonia (CD), repeated injections of incobotulinumtoxinA at intervals as early as 6 weeks after a previous treatment, based on individual patient need, were effective and well tolerated. Here, the BoNT doses and dosing intervals currently indicated in the USA and European Union are reviewed, together with the use of BoNT for the treatment of spasticity, CD, and blepharospasm. Opportunities for tailored BoNT therapy are also discussed.

1. Introduction

Botulinum neurotoxin type A (BoNT-A) injection is the recommended first-line treatment for focal hyperkinetic movement disorders such as cervical dystonia (CD) and blepharospasm (BSP) (Albanese et al., 2015; Simpson et al., 2016), and is recommended as an effective part of multi-modal treatment for focal and segmental upper- and lower-limb spasticity in adults (Baker and Pereira, 2013; Esquenazi et al., 2017; Simpson et al., 2016; Wissel et al., 2009). Usually botulinum neurotoxin (BoNT) can be used for the focal treatment of muscles involved in focal dystonia in close anatomical proximity in the face, arm, or neck region (Albanese et al., 2015; Hallett et al., 2009) and, in the treatment of focal or segmental spasticity, at one-to-three movement segments in limbs, such as the hand, forearm, and shoulder, or the foot, ankle, and knee (Simpson et al., 2017; Wissel et al., 2009). A wealth of clinical experience has demonstrated that BoNT is very much a long-term and individualized treatment (Kaňovský et al., 2009, 2011; Kessler et al., 1999; Mohammadi et al., 2010; Schramm et al., 2014). By modifying the target muscles for therapy, the BoNT dose (per session, per muscle, and/or per injection site), the interval between treatments (Albanese et al., 2015) and the number of target sites (single joint vs multiple movement segments) (Wissel et al., 2009), focal and segmental BoNT treatment can be tailored to individual patients' symptoms. However, muscle selection and dosing are based on the clinical experience of the treating physician (Albanese et al., 2015), and a single approach does not suit all patients, even within one disease indication.

Although BoNT is an effective treatment option for many movement disorders, and studies show that BoNT treatment reduces symptom burden and disability, thereby increasing patient participation in daily activities and improving quality of life (Dressler et al., 2015b; Hefter et al., 2013; Rychlik et al., 2016), the degree of flexibility in treatment protocols is determined by individual product licenses, which often lag behind experience from real-world clinical practice (Schramm et al., 2014) and in the context of clinical studies (Hyman et al., 2000; Pittock et al., 2003; Poewe et al., 1998; Wissel et al., 2017). Several patient/practitioner surveys and an online discussion forum conducted during the last few years have highlighted a desire for more tailored treatment options and more flexibility in dose and/or injection intervals than

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Abbreviations

BoNT	botulinum neurotoxin
BoNT-A	botulinum neurotoxin type A
BSP	blepharospasm
CD	cervical dystonia
UMNS	upper motor neurone syndrome

those currently approved (Bensmail et al., 2014; Poliziani et al., 2016; Sethi et al., 2012). However, despite more than 25 years of clinical experience and numerous guidelines, product licenses, and recommendations for dosing and intervals, there is insufficient evidence from well-designed clinical trials to support higher-than-labelled doses of BoNT per treatment session and individualized treatment intervals, or to inform changes to product licenses (Simpson et al., 2016). Here, the BoNT doses and dosing intervals currently indicated in the USA and European Union are reviewed, together with the use of BoNT for the treatment of spasticity, CD, and BSP, and the opportunities for tailoring BoNT therapy to meet individual patients' needs for these conditions are discussed.

2. BoNT mechanism of action in dystonic and spastic movement disorders

Dystonia is a movement disorder characterized by slow, typically patterned, twisting, repetitive movements or abnormal postures that are often accompanied by pain and tremor, and are caused by involuntary muscle contractions (Albanese et al., 2013). There are many types of dystonia with differing and overlapping pathophysiologic features, and clinical diagnostic criteria to characterize the individual subtypes remain an unmet need (Albanese, 2017). The most common focal dystonia is CD (Epidemiological Study of Dystonia in Europe [ESDE] Collaborative Group, 2000), also known as spasmodic torticollis (Chan et al., 1991). CD is characterized by abnormal head, neck, and shoulder posture caused by contraction of the cervical muscles, which may be accompanied by involuntary movements that are sometimes tremulous (Albanese et al., 2015; Chan et al., 1991), and the diagnosis of CD is considered an easy one, based on clinical experience (Albanese, 2017). The second most frequent focal dystonia is BSP (Epidemiological Study of Dystonia in Europe [ESDE] Collaborative Group, 2000), a cranio-facial dystonia characterized by repetitive, bilateral, involuntary contraction of the orbicularis oculi, resulting in spasmodic eyelid contraction, which forms the basis of diagnosis (Defazio et al., 2013).

Spasticity, defined by Young in 1994 (Young, 1994), is only one component of the upper motor neurone syndrome (UMNS) (Wissel et al., 2009). UMNS occurs following a lesion in the cerebrum or spinal cord that alters sensorimotor structures, and can be caused by stroke, spinal-cord injury, brain injury, or other neurologic conditions and neurodegenerative diseases (Wissel et al., 2009). In everyday clinical use, the term “spasticity” collectively describes a combination of clinical signs and was originally defined by J.W. Lance in the 1980s as, “*a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the UMNS*” (Lance, 1980). In 2005, Pandyan et al. redefined spasticity as, “*disordered sensori-motor control, resulting from an UMN lesion, presenting as intermittent or sustained involuntary activation of muscles*”, focusing on the positive features (characterized by increased levels of involuntary motor activity) of the UMNS, while excluding the negative features (characterized by reduced levels of voluntary motor activity) of the syndrome and the biomechanical alterations in joints and soft tissue (Pandyan et al., 2005).

The clinical features and changing understanding of dystonia (Albanese et al., 2013; Albanese, 2017; Phukan et al., 2011) and spasticity (Trompetto et al., 2014; Wissel et al., 2009) have been reviewed extensively in the literature. Although distinct conditions, dystonia and spasticity have common traits, including the characteristic involuntary muscle hyperactivity and co-contractions that may lead to disturbed movement performance, involuntary movements, spasms, and altered joint positions due to imbalance of antagonistic muscles, resulting in disfigurement and pain. Muscle hyperactivity can be effectively targeted by BoNT therapy through acetylcholine blockade at the neuromuscular junction with blockade of the extra- and intra-fusal muscle fibers and nerve terminals, as reviewed by Dressler and Adib Saberi (2005) and Kumar et al. (2016). However, the effects of BoNT treatment are temporary, which may be attributed to the re-establishment of synaptic contacts with the denervated muscle through a proposed mechanism of motor-neurone sprouting (de Paiva et al., 1999). The duration of BoNT treatment effect varies from patient to patient, from 9–10 to over 17 weeks (Marsh et al., 2014; Sethi et al., 2012) with a mean duration of 13.2–13.5 weeks in patients with CD (Marsh et al., 2014) and a mean (standard deviation) duration of 9.3 (4.0) weeks in patients with post-stroke spasticity (Bensmail et al., 2014). Dose-dependent effects of BoNT treatments have also been documented, with increasing doses of BoNT being associated with the greatest effects on muscle tone in patients with post-stroke spasticity (Pittock et al., 2003; Yablon et al., 2011).

Common adverse events associated with BoNT treatment include injection-site pain and diffusion of the toxin from the injection site into neighbouring muscles causing inadvertent weakness, with symptoms including: dysphagia, following injection of the neck muscles; ptosis, following injection of the orbicularis oculi; and weakness of adjacent muscles, following injection of the limb muscles (Allergan Inc., 2017; Ipsen Biopharm Ltd, 2017; Merz Pharmaceuticals LLC, 2015; Solstice Neurosciences Inc, 2009). However, a wealth of clinical evidence is accumulating to show that BoNT treatment is well tolerated, and typically associated with few adverse events, which are generally transient and mild-to-moderate in severity (Dong et al., 2017; Naumann and Jankovic, 2004).

3. BoNT treatment of dystonia and spasticity

Licensed indications for BoNT treatment, dosing, and injection intervals are influenced by the regulatory authorities in different countries. Three BoNT-A formulations (onabotulinumtoxinA, Botox®, Allergan Inc; abobotulinumtoxinA, Dysport®, Ipsen Biopharm Ltd; incobotulinumtoxinA, Xeomin®, Merz Pharmaceuticals GmbH) and one BoNT type-B formulation (rimabotulinumtoxinB, Myobloc®/NeuroBloc®, Solstice Neurosciences Inc/Eisai Ltd) are currently approved in the USA and European Union for the treatment of dystonia and/or spasticity. Table 1 provides a snapshot of the current US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approval (focusing on UK approval as an example) for these formulations as they relate to the treatment of dystonia and spasticity in adults. Similarities and differences in clinical indications, BoNT doses, and dosing intervals between regions and formulations are highlighted. The level of clinical evidence referred to in currently available US and European guideline recommendations is included in Table 1 for comparison. There are several national and international guidelines and consensus statements relating to the use of BoNT in spasticity and dystonia, which are based on clinical evidence and

Table 1
Total approved doses, injection intervals and recommendations for the use of BoNT formulations for the treatment of dystonia (blepharospasm, cervical dystonia) and spasticity (upper and lower limb) in adults.

			US			EU		
Indication	BoNT formulation	Brand name (manufacturer)	Approved dose[a, b, c, d]	Approved interval[a, b, c, d]	Guideline recommendation, evidence class[i]	Approved dose[e, f, g, h]	Approved interval[e, f, g, h]	Guideline recommendation, evidence class[j]
Cervical dystonia	OnabotulinumtoxinA	Botox® (Allergan Inc)	Up to 400 U	≥12 weeks	Level B	Up to 300 U	≥10 weeks	Class I/Ia
	AbobotulinumtoxinA	Dysport® (Ipsen Biopharm Ltd)	250–1000 U[1]	≥12 weeks	Level A	250–1000 U	≥12 weeks	Class I/Ia
	IncobotulinumtoxinA	Xeomin® (Merz Pharmaceuticals GmbH)	120–240 U[2]	≥12 weeks	Level B	Up to 300 U[3]	≥10 weeks	Class I/Ia
	RimabotulinumtoxinB	Myobloc®/NeuroBloc® (Solstice Neurosciences Inc/Eisai Ltd)	2500–5000 U	≥12 weeks	Level A	≤10,000 U[4]	≥12 weeks	Class I/Ia
Blepharospasm	OnabotulinumtoxinA	Botox® (Allergan Inc)	200 U	≥12 weeks	Level B	Up to 100 U	≥12 weeks	
	AbobotulinumtoxinA	Dysport® (Ipsen Biopharm Ltd)	NA		Level C	240 U (up to 120 U per eye)	≥12 weeks	
	IncobotulinumtoxinA	Xeomin® (Merz Pharmaceuticals GmbH)	70 U (35 U/eye)[5]	≥12 weeks	Level B	100 U (25–50 U per eye)	≥12 weeks	
	RimabotulinumtoxinB	Myobloc®/NeuroBloc® (Solstice Neurosciences Inc/Eisai Ltd)	NA		Level U	NA		
Upper-limb spasticity	OnabotulinumtoxinA	Botox® (Allergan Inc)	Up to 400 U	≥12 weeks	Level A	200–240 U[6]	≥12 weeks[6]	Class Ib
	AbobotulinumtoxinA	Dysport® (Ipsen Biopharm Ltd)	500–1000 U	≥12 weeks	Level A	500–1000 U	≥12 weeks	Class Ib
	IncobotulinumtoxinA	Xeomin®(Merz Pharmaceuticals GmbH)	Up to 400 U	≥12 weeks	Level A	Up to 400 U[6]	≥12 weeks[6]	
	RimabotulinumtoxinB	Myobloc®/NeuroBloc® (Solstice Neurosciences Inc/Eisai Ltd)	NA		Level B	NA		
Lower-limb spasticity	OnabotulinumtoxinA	Botox® (Allergan Inc)	300–400 U	≥12 weeks	Level A	300 U[6]	≥12 weeks[6]	Class Ib
	AbobotulinumtoxinA	Dysport® (Ipsen Biopharm Ltd)	≤1500 U	≥12 weeks	Level A	≤1500 U[7]	≥12 weeks[7]	Class Ib
	IncobotulinumtoxinA	Xeomin® (Merz Pharmaceuticals GmbH)	NA		Level U	NA		
	RimabotulinumtoxinB	Myobloc®/NeuroBloc® (Solstice Neurosciences Inc/Eisai Ltd)	NA		Level U	NA		

Approval in the United Kingdom is cited as a general example of EU approval. Total approved doses and minimum injection interval are shown for selected product indications as they relate to the treatment of spasticity, blepharospasm and cervical dystonia in adults. See Summaries of Product Characteristics for full product indications.[a–h] Doses should be divided between the muscles for treatment.
BoNT, botulinum neurotoxin; EU, European Union; NA, not approved; US, United States.
[1]Initial recommended dose 500 U.
[2]Initial recommended dose 120 U. Initial doses of 120 U and 240 U were used in clinical trials.
[3]A maximum of 50 U at any one injection site.
[4]Initial dose 10,000 U. Initial dose of 5000 U may also be considered.
[5]Indicated for patients previously treated with onabotulinumtoxinA.
[6]Indicated for post-stroke spasticity.
[7]Indicated for upper-limb spasticity and lower-limb spasticity affecting the ankle joint as a result of stroke or traumatic brain injury.
[a]Allergan Inc. Highlights of prescribing information – Botox®, April 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf.
[b]Ipsen Biopharm Ltd. Highlights of prescribing information – Dysport®, June 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125274s109lbl.pdf.
[c]Merz Pharmaceuticals LLC. Highlights of prescribing information – Xeomin®, December 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125360s067lbl.pdf.
[d]Solstice Neurosciences Inc. FDA-approved labelling – Myobloc®, July 2009. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103846s5120lbl.pdf.
[e]Allergan Ltd. Botox® 100 U Summary of Product Characteristics, March 2017. Available at: http://www.medicines.org.uk/EMC/medicine/112/SPC/.
[f]Ipsen Ltd. Dysport® 300 U Summary of Product Characteristics, July 2017. Available at: http://www.medicines.org.uk/EMC/medicine/870/SPC/.
[g]Merz Pharma UK Ltd. Xeomin® 100 U Summary of Product Characteristics, July 2016. Available at: https://www.medicines.org.uk/emc/medicine/20666.
[h]Eisai Ltd. NeuroBloc® 5000 U Summary of Product Characteristics, April 2017. Available at: http://www.medicines.org.uk/emc/medicine/20568.
[i]Simpson et al., 2016.
[j]Albanese et al., 2015; Wissel et al., 2009.

expert opinion at the time of compilation (Albanese et al., 2015; Esquenazi et al., 2017; Hallett et al., 2009; Sheean et al., 2010; Simpson et al., 2016, 2017; Wissel et al., 2009). Both product licenses and guideline recommendations often lag behind real-world clinical experience; for example, there has been no change to the BoNT dosing recommendations for BSP for over two decades. Furthermore, the authors of a European consensus statement on the management of CD stated that evidence for a fixed injection interval of 12 weeks in patients with CD was lacking and that patients may benefit from more flexible and individualized treatment (Albanese et al., 2015). Current practice towards individualized treatment goes well beyond existing labelling restrictions. As discussed below, new evidence following research conducted in the last few years shows that the thinking around how patients are treated has evolved and opens new avenues for treatment.

4. BoNT treatment of dystonia and spasticity in clinical practice

Evidence has shown that clinical efficacy is improved when muscle selection for BoNT injections is performed by experienced clinicians under appropriate guidance techniques, such as ultrasound (Picelli et al., 2012, 2014), motor point/endplate targeting, or electromyography (Wissel et al., 2009), to ensure accurate placement of the toxin. Furthermore, BoNT is recommended as part of a multi-disciplinary approach involving synergistic treatments (casting, splinting, physiotherapy, occupational therapy, and robotics) performed by teams of physical medicine and rehabilitation specialists (Sheean et al., 2010; Simpson et al., 2017; Wissel et al., 2009). Data suggest that the clinical efficacy of BoNT may also be improved by combining treatment with rehabilitation measures such as stretching in comparison with BoNT treatment alone (Kinnear et al., 2014). Additionally, certain factors can be adapted to tailor treatment to individual patient needs, including injection sites per muscle and dilution of the toxin (Gracies et al., 2009). Two key factors are modulation of the BoNT dose administered per injection session and the interval between consecutive doses, discussed below.

4.1. Modulation of BoNT dose

A survey conducted in Europe and North America showed that overall patient satisfaction with BoNT-A treatment for post-stroke spasticity was very high, with the highest levels of satisfaction being associated with peak efficacy of the toxin (Bensmail et al., 2014). However, when asked what percentage of patients would benefit “very much”, “moderately”, or “not at all” from higher-than-labelled BoNT doses, physicians estimated that therapy outcome and patient satisfaction could be improved in 75.8% and 78.8% of patients with post-stroke spasticity, respectively (Bensmail et al., 2014). Similarly, in an international survey in Europe, Canada, Mexico, and Russia, 60.9% of physicians stated that they would inject higher doses of BoNT for the treatment of spasticity if indicated (Harriss et al., 2014). Unpublished data from this investigation indicate that physicians would inject mean doses of incobotulinumtoxinA 651 U, onabotulinumtoxinA 640 U, and abobotulinumtoxinA 1751 U if indicated (Harriss et al., 2016) (poster presented at TOXINS 2017) compared with maximum approved doses of 400 U, 400 U, and 1000 U for incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, respectively in the USA (Table 1), highlighting a discrepancy between currently approved doses and those desired in clinical practice.

Post-stroke spasticity is a significant health problem negatively impacting the quality of life of stroke survivors (Doan et al., 2012; Gillard et al., 2015). In most patients with post-stroke spasticity, both upper- and lower-limb function are affected (Watkins et al., 2002). One challenge of treating multi-focal spasticity is that the BoNT doses required to treat all spasticity patterns effectively may exceed the maximum doses currently approved for each treatment cycle (Wissel et al., 2017). Furthermore, BoNT treatment of the lower limb is not covered by all product licenses (Table 1). Although patient and practitioner surveys provide important information relating to patient needs, more large-scale prospective studies investigating different BoNT treatment protocols are required to inform any potential changes to product licences.

The tolerability of higher-than-labelled doses of BoNT has been reported (Baricich et al., 2015; Dressler et al., 2015a; Intiso et al., 2014; Santamato et al., 2013, 2015), but not studied extensively in large prospective trials, until recently. The TOWER study was a prospective, open-label, single-arm, multicenter, dose-titration study that primarily investigated the safety, but also the efficacy, of higher BoNT doses than used previously. Total-body doses of incobotulinumtoxinA, from the maximum approved upper-limb dose of 400 U up to 800 U, were administered during three injection cycles in 155 patients with upper- and lower-limb spasticity of the same body side due to cerebral lesions (Wissel et al., 2017), allowing the combined treatment of both upper- and lower-limb spasticity patterns. In Cycles 1 and 2, patients received 400 U and 600 U, respectively, into the upper and/or lower limb. In Cycle 3, patients received total-body doses of 800 U into both the upper and lower limbs. A maximal total dose of 600 U per limb was administered and each injection cycle was followed by 12–16 weeks of observation.

Over 93% of patients received doses of $\geq$700 U in Cycle 3 (Wissel et al., 2017), and escalating incobotulinumtoxinA doses were effective and well tolerated. There was no increase in the incidence of adverse events with increasing dose or repeated injections and no secondary non-response due to neutralizing antibodies. Results showed a significant improvement in mean resistance to passive movement between the injection cycle baseline and 4 weeks post-injection in all cycles ($P < 0.0001$), which increased throughout the study. In addition, the proportion of patients achieving at least three of a possible four treatment goals increased at each injection cycle (25.2%, 50.7%, and 68.6% at Cycles 1, 2, and 3, respectively) (Wissel et al., 2017). Results of the TOWER study support the conclusion that escalating incobotulinumtoxinA total-body doses (up to 800 U) allows the treatment of an increasing number of spasticity patterns at a single treatment session without compromising safety or tolerability. However, more prospective studies with incobotulinumtoxinA and other BoNT formulations are required to confirm this result.

4.2. Modulation of intervals between BoNT injections

Early retrospective studies found a correlation between higher cumulative doses of BoNT in patients with CD and the incidence of neutralizing antibodies, particularly when patients received higher doses per treatment or top-up injections at intervals of <4 weeks (Greene et al., 1994; Jankovic and Schwartz, 1995). This invoked caution in terms of injection intervals and forms the basis for the currently approved injection intervals (Albanese et al., 2015) (Table 1). However, these results may reflect the lack of purity in early onabotulinumtoxinA formulations (Jankovic et al., 2003), which led to up to 23% of patients developing neutralizing antibodies (Jankovic and Schwartz, 1995).

A subsequent study in patients with CD showed that abobotulinumtoxinA injected at approximately 3-monthly intervals was well tolerated and resulted in sustained disease management over more than six treatment cycles. There was no incidence of new adverse events and neutralizing antibodies were detected in 2% of

patients, although a further 5% experienced clinical non-responsiveness (Kessler et al., 1999).

Although BoNT treatment is effective, the effects are temporary and many patients experience waning and re-emergence of symptoms before the end of the treatment cycle (Dressler et al., 2015c). Consistent with this, and despite recommendations for a minimum interval of 10–12 weeks between injections for the treatment of dystonia and 12 weeks for spasticity, evidence from a survey of patients with post-stroke spasticity suggests that shorter intervals between BoNT treatments would be preferred by many patients (Bensmail et al., 2014). When asked if, given the choice, they would have liked a re-injection on the day of the interview (7–10 weeks since the last injection), >73% of patients would have preferred re-injection at this point. When specifically asked about their preferred treatment interval, 43.4% of patients would have preferred treatment intervals of <10 weeks (Fig. 1) (Bensmail et al., 2014). A similar survey conducted in patients with CD reported that 45.6% of patients would have preferred treatment intervals of ≤10 weeks and the median preferred interval ranged from 10–12 weeks (Sethi et al., 2012).

While shorter injection cycles may be used in clinical practice for BoNT treatment of spasticity, there are no prospective safety and tolerability data available to support such an amendment to the recommended treatment schedule. However, three prospective studies of incobotulinumtoxinA treatment conducted in CD (Comella et al., 2011; Evidente et al., 2013) and BSP (Truong et al., 2013) showed that incobotulinumtoxinA treatment was effective and well tolerated, with no new or unexpected safety concerns following repeated injections at intervals based largely on patient requirement. Re-injections could be performed as early as 6 weeks after a previous treatment if patients spontaneously requested it and if retreatment was deemed necessary by clinical assessment (Evidente et al., 2013; Truong et al., 2013).

Post-hoc analysis showed that 44.9% of a total of 821 incobotulinumtoxinA injections in patients with CD and 44.9% of a total of 461 injections in patients with BSP were given at injection intervals <12 weeks (Evidente et al., 2014) (Fig. 2). Importantly, with flexible injection intervals (6–20 weeks), the incidence of adverse events did not change when injection intervals were

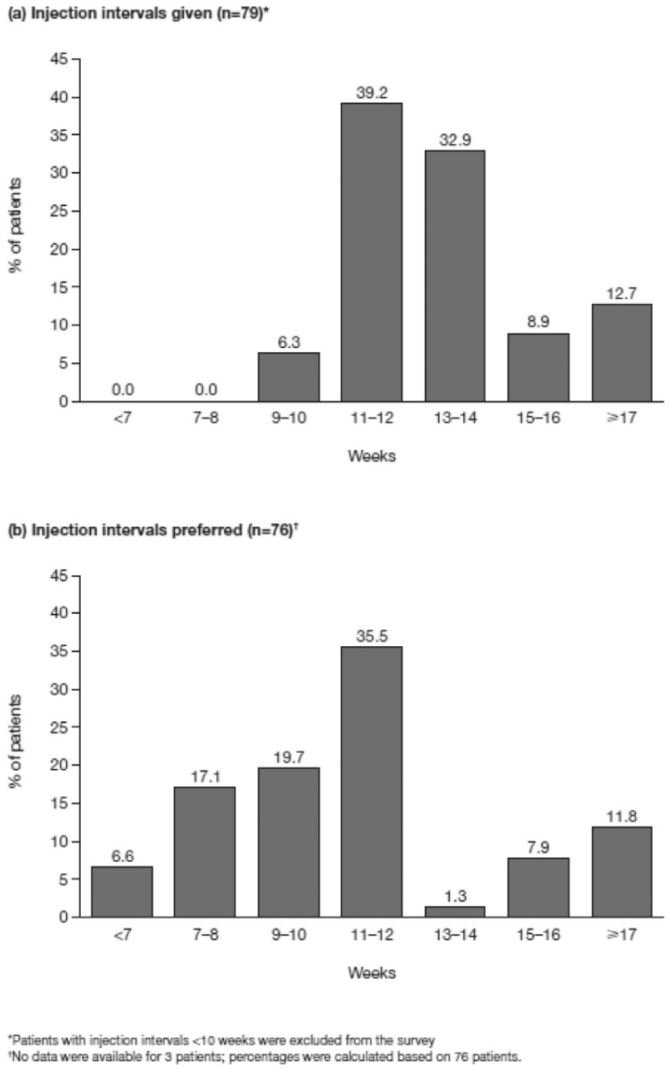

Fig. 1. Patient survey – preferred versus actual injection intervals for BoNT treatment of post-stroke spasticity, Bensmail D et al. *Journal of Medical Economics,* September 2014. Satisfaction with botulinum toxin treatment in post-stroke spasticity: Results from two cross-sectional surveys (patients and physicians). Reprinted by permission of the publisher Taylor & Francis Ltd (http://www.tandfonline.com/).

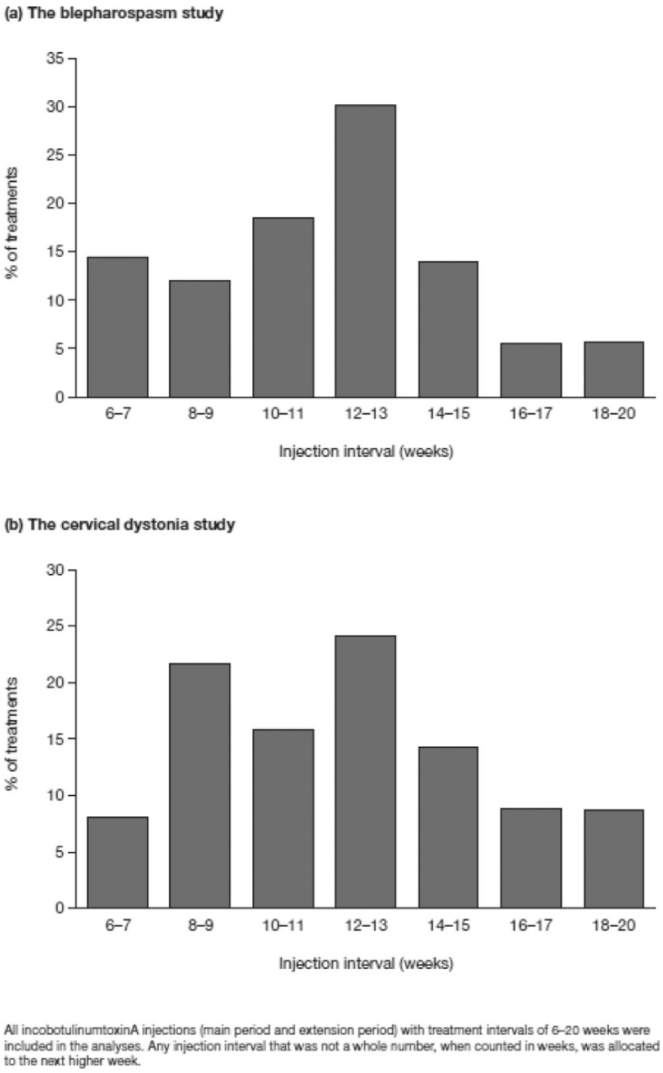

Fig. 2. Post-hoc analysis data of incobotulinumtoxinA injection intervals received in response to clinical need in patients with blepharospasm and cervical dystonia. Reprinted with permission from Evidente VGH et al. *Journal of Neurological Sciences* 2014.

adjusted and there was no increase in the proportion of patients developing neutralizing antibodies at trial termination versus baseline (Evidente et al., 2013).

5. Summary

Individualized treatment of dystonic and spastic movement disorders may be enabled with BoNT treatment. However, there is a desire for greater flexibility in total-body doses and injection intervals than those currently approved.

Results of the first prospective trial that investigated the safety of higher-than-labelled BoNT doses as a primary outcome measure in patients with spasticity are now available and argue for more flexibility in dosing to allow higher total-body doses and more spastic patterns to be treated per session (Wissel et al., 2017). Furthermore, reliable data are now available that argue for more flexible, individualized intervals between BoNT injections to allow maximum benefit in patients receiving focal BoNT treatment for CD and BSP (Comella et al., 2011; Evidente et al., 2013, 2014; Truong et al., 2013).

Interesting times lie ahead for the management of spasticity, dystonia, and other movement disorders. Recent evidence offers new opportunities for individualized BoNT treatment; however, more large-scale prospective studies with different BoNT formulations in different patient populations are required.

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Transparency document

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