Chapter 15
Why Neurotoxin Treatment is Generally Safe? What is the Long-Term Efficacy

Botulinum Neurotoxin (BoNT), produced by the bacteria- clostridium botulinum, is one of the most potent bacterial toxins known to mankind. These bacteria are present in the nature and eating food contaminated by this toxin causes a serious disease called botulism. In older days, most cases of botulism were fatal. Currently, with availability of modern intensive care units and the level of respiratory support, most patients survive if diagnosed early.

The patients' safety with BoNT therapy, has been a concern since the early days of Botox's introduction as an injectable medicinal agent by Allan Scott in 1970s (Chap. 1). Animal studies were conducted to define dangerous dose levels with Botox treatment. In monkeys with comparable body size to human, injection of 3000 units of Botox was found to be lethal. This suggested a level of safety for the early FDA approved indications of Botox therapy such as injections of small eye muscles (for correction of crossed eyes) and for involuntary facial movements (facial spasms). In these conditions, the total dose of Botox injected per session was often below 50 units since the muscles were of small size.

A new era of concern began with emerging indications of botulinum therapy for larger muscles such as neck and shoulder muscles in case of cervical dystonia (involuntary movements and postures of neck and shoulder (see Chap. 11) and when BoNTs were used for large limb muscle of the patients with spasticity. Spasticity (increased muscle tone with muscle stiffness) can occur as the result of such common neurological problems as stroke, multiple sclerosis and trauma to the brain and spinal cord (see Chaps. 6, 7). With FDA approval of BoNT therapy for cervical dystonia and spasticity, these two conditions became the most frequent indications for BoNT therapy. It soon became apparent that many patients with these two conditions, specially spasticity, require doses larger than a couple of hundred units. Allan Scott's limited observations in 1980's showing no serious side effects with Botox doses of up to 300 units (in spasticity), suggested that doses higher than 300 units may be safe in human subjects. Currently, three BoNTs, Dysport, Botox and Xeomin are approved by FDA for treatment of spasticity (see Chap. 3 for details). Dysport is the only drug that is approved for lower limb

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spasticity in children. In addition to these type A toxins, FDA has approved also a type B toxin (Myobloc) for treatment of cervical dystonia. Currently, only type A and B toxins are suitable for clinical use. For description of type A and B toxin's characteristics, the reader is referred to Chaps. 2 and 3 of this book.

Since the units of BoNTs are not truly interchangeable, the safety issues with BoNTs need to be addressed in the context of the particular BoNT used. The following, is an approximation of units among toxins: 1 Botox unit = 1 Xeomin unit = 2.5 Dysport unit = 40–50 Myobloc unit. Other FDA approved indications of BoNT therapy consist of chronic migraine (Botox), bladder dysfunction (Botox), facial lines and cosmetics (Botox, Xeomin, Dysport), autonomic disorders such as excessive perspiration or salivation/drooling (Botox, Xeomin, Dysport) and strabismus/squint (Botox).

The safety issues with BoNTs are twofold;

1. The presence of small amount of human serum albumin as a component of BoNT preparation could potentially cause problems. It is known that a virus like agent -Prion that causes a very rare, but devastating neurological disorder can potentially be transmitted from human to human through injections of human serum albumin. The disease is called Creutzfeld- Jacob disease (CJ) named, after two physicians who first described it. It leads to mental deterioration, seizures and incapacity. At the end of 20th century, a variant of CJ virus caused "mad cow "- disease in England and Europe. To date, after almost 30 years of Botox therapy, the past 15 years of which has included many millions of injections worldwide, there has not been any documented case of CJ disease that could be related to Botox injections. It is therefore, generally, believed that the chance of getting CJ- disease from Botox treatment is extremely remote.
2. The side effect related to the main mechanism of action of Botox and other BoNTs namely blocking the release of acetylcholine from the nerve-muscle junction. Acetylcholine, a well- known chemical, is released at nerve endings after receiving signals from brain to activate the muscle. Through this function, BoNT injections into muscles improve and reduce involuntary movements and muscle stiffness as well as spasticity secondary to brain trauma or stroke. The effect of any type of botulinum toxin after an intramuscular injection, usually lasts for 3 to 4 months. However, if the effect of injected BoNT over nerve-muscle junction is excessive, instead of inducing a mild weakening that has a therapeutic, good effect, the muscle may lose completely its function and become paralyzed. Focal loss of muscle function for weeks or months is troublesome and, in case of paralysis of muscles involved in swallowing may require feeding through the nose and close monitoring to avoid aspiration. This is also a concern when the neck muscles are injected, especially in inappropriate sites or with inappropriately large doses. If the muscle weakness caused by BoNT injection is severe and it extends beyond the injected muscle to affect many muscles in the body, it can theoretically cause botulism. Botulism can be fatal as it can affect the breathing muscles, requiring respiratory support in the intensive care unit. Regarding these concerns, in 2009, FDA inserted a black box warning in all

botulinum toxin brochures indicating the danger of potential spread and serious complications with botulinum toxin therapy and serious complications.

Over the past 15 years, several studies have focused on assessing the safety of BoNT injections in adults and children. A summary of some high- quality studies (placebo controlled) with sizeable number of studied patients (>50) and their conclusions regarding safety are presented in the following pages.

BoNT Studies of Spasticity in Adults

Dr. Gracies and his co-workers studied 156 patients with Dysport injections into spastic muscles of the leg that had developed secondary to stroke or head trauma [1]. The patients were divided into three groups receiving either placebo or Dysport 1000 and Dysport 1500 units. Each group consisted of 52 patients. The study was double-blind (both physician and patient) and placebo controlled. It was conducted in multiple centers. The positive impact of Dysport in improving spasticity and patients' quality of life resulted in subsequent approval of Dysport by FDA for use in the US for lower limb spasticity (2017). The authors reported that side effects were slightly more in the toxin group compared to the placebo, but there were no serious side effects. Three patients developed transient swallowing difficulties and three had mild transient diffuse muscle weakness. Furthermore, in a subsequent analysis of a subgroup of this study who had paralysis in one side with spasticity due to stroke or trauma, Dr. Marciniac and her co-workers also found also no serious side effects. The most common side effect was transient inflammation of the nose and throat (pharyngitis); this side effect was found in 5.7% of the toxin groups [2].

In another study published in 2015, the authors assessed the efficacy of Dysport in three group of patients, each consisting of 81 patients who received Dysport injections of 500 and 1000 units and saline injections [3]. Patients had muscle spasticity (stiffness and increased tone) secondary to stroke or trauma. Although side effects were higher in the two toxin groups- 7% and 9% in low and high dose groups, respectively, compared to 2% observed in the placebo group- there were no serious side effects. The most common side effect in the toxin groups was mild and transient muscle weakness.

Dr. Elovic and his co-workers conducted a blinded and placebo- controlled study with Xeomin in 317 patients with adult upper limb spasticity [4]. Xeomin and saline (placebo) were injected into the muscles of 210 and 107 patients, respectively. Xeomin is another type A, FDA approved BoNT with units comparable to Botox. The following doses were used for different areas of the upper limbspasticity; flexed elbow, 200 units- flexed wrist, 150 units- clinched fist, 100 units. Authors noted significant improvement of spasticity and quality of life in patient who received Xeomin. No serious treatment -related side effect was noted in any patient. The most common side effect was dryness of the mouth which was noted in 4 patients in the Xeomin group and 1 patient in the placebo group.

In 2003, Dr. Pittock and his colleagues published a study in which intramuscular injection of Dysport was compared with placebo in 243 patients with stroke related spasticity [5]. Patients were divided into 4 groups; one group received placebo (saline) and the other three received three doses of Dysport, 500, 1000, 1500, respectively. The study was double- blind meaning neither the patient nor the injecting physician knew what was injected into the muscle. The study showed that Dysport injections reduced muscle stiffness and muscle pain as well as the use of walking aids. No serious side effects related to treatment was reported. The frequency of adverse effects was comparable between Dysport groups and the placebo group ranging from 29 to 33%. Most adverse effects were mild or not related to treatment. Two concerning adverse effects, were reported as "severe" in the Dysport group; one patient developed difficulty in swallowing and the other demonstrated deterioration of walking. The authors did not report how long these symptoms lasted.

In another study, asessing the efficacy of Botox in ankle flexor spasticity, the authors injected 200 and 300 units of Botox into the muscles that flex and invert the foot [6]. Patients had pain in calf muscles and difficulty in standing and walking. Botox injection reduced patients' pain and improved their walking. Authors noted 22 non-serious adverse effects, unrelated to treatment. There was no difference between the Botox and placebo group regarding the frequency of adverse effects.

Dr. Wein and his colleagues conducted a large multicenter study with Botox evaluating the effectiveness of this toxin formulation in reducing spasticity and pain [7]. The study had two arms; the first being blinded (comparing Botox effect with placebo) and the second phase was open label (no placebo), further assessing effectiveness of Botox over one year. The first study included 468 and the second study 407 patients. These researchers found that injection of 300 and 400 units of Botox into the leg muscles improved muscle pain and reduced abnormally high muscle tone along with significant improvement of leg function. Treatment related adverse effects were noted in 10% of the toxin group versus 7.1% of the placebo (saline) group (no statistically significant difference). None of the treatment related adverse effects were considered serious. Pain at the site of injection and nasopharyngitis were the two most common side effects but occurred with comparable frequency in the toxin and placebo groups. For Botox and Xeomin, FDA approved an upper limit of 400 units per session for treatment of upper limb spasticity (approximately 1000 units of Dysport).

The above reported low incidence of serious side effects in the BoNT (Botox, Dysport, Zeomin) injected patients conducted on large number of patients with spasticity encouraged researcher to study the safety of doses higher than 400 units for this indication. In practice, many stroke or trauma patients have severe spasticity in more than one limb and 400 units of Botox or Xeomin may not be enough to cover two or three limbs.

Dr. Dressler and his colleagues researched the safety of high doses of Xeomin (> 400 units) which was injected to 100 adult patients, half with spasticity and half with involuntary movements [8]. Xeomin is a FDA approved BoNT with units comparable to Botox. In most patients, the injected dose was between 410 to 700 units

(average 570 units). Two patients received 1000 units and 4 patients received 1200 units. Close to half of the patients reported mild side effects but, except difficulty in swallowing, none appeared to be related to BoNT treatment. This side effect was noted in 8% of the patients with cervical dystonia (involuntary neck movements). None of the patients with spasticity, even those few, that had received the highest doses of 1000 and 1200 units showed any systemic reactions or manifested any signs suggestive of botulism.

In a more recent study, Wissel and co-workers have demonstrated that escalation of Xeomin doses from 400 units to 600 and to 800 units in patients with spasticity is well tolerated and produced no serious side effects [9]. The study group consisted of 155 patients who developed limb spasticity secondary to brain damage. One upper limb was injected during the study. Treatment related adverse effects included pain in the injected limb (3 patient), mild difficulty in swallowing and diffuse muscle weakness (2 patients each). Double vision, constipation, slowing of heart rate was noted in one patient each. All adverse effects resolved in 4–6 weeks.

BoNT Studies of Spasticity in Children

Spasticity is a major handicap for small children affected by conditions that damage the brain and spinal cord during neonatal period, infancy and childhood. The leading causes of spasticity in children are cerebral palsy, and trauma to the nervous system, as well as genetic disorders that affect the brain from early childhood (see Chap. 14). As the emerging studies demonstrate that childhood spasticity may improve with escalation of the dose of injected botulinum neurotoxin, the issue of child's safety becomes a prime point of focus and concern for researchers and clinicians who work in this field. Researchers tried to establish a safe ceiling for the total dose of toxin used for treatment of spasticity. This safety ceiling is represented as units of injected toxin per/Kg of body weight. Dr. Kat Kloski's recent publication [10], discusses safety issues in childhood and includes the figure below showing the escalation figures for the maximum dose for children published by researches since 1993 (Fig. 15.1).

Table 15.1, represents the safety data described in the high quality publications (comparing toxin with placebo) regarding the use of BoNT therapy in children for the past 20 years.

The aforementioned data from well-crafted and high quality studies indicate that serious and life threatening side effects are exceedingly rare in botulinum toxin treatment of spasticity. Hence, the four US marketed BoNTs (Botox, Xeomin, Dysport, Myobloc) can be considered generally safe for treatment of spasticity in adults and children. However, since serious side effects have been reported to FDA (mostly from case observations and low- quality data), the injector needs to be alert to such rare occurrences. In rare cases, spread to remote sites may occur leading to such symptoms as difficulty in swallowing after injection of a limb muscle. In high quality studies of spasticity, however, most such cases has been mild and self-limiting.

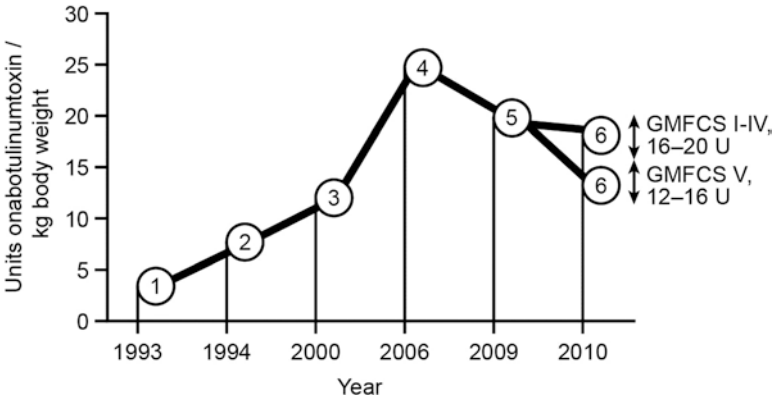

Fig. 15.1 The ceiling dose of Botox used by researchers in various publications since 1993. From Stroble and co-workers published in Toxins 2015. Reproduced with permission from publisher, MDPI

Familiarity with anatomy of the muscles, characteristics of different toxins and relative dose equivalencies among toxins is a knowledge that is essential for treatment of spasticity. In children, study of the maximum safe dose toxin dose per session is an evolving research issue. Based on current literature, most injectors believe that a maximum dose of 15–16 units per Kg of body weight per session is safe.

Botulinum Toxin Treatment of Cervical Dystonia in Adults

Cervical dystonia is mainly an adult disorder, usually presenting after age 40 years. Patients' involuntary movements (dystonia) manifest as twisting and turning of the neck and shoulder muscles. Abnormal postures of the neck such as turning or tilting to one side are common features of this disorder. After spasticity, cervical dystonia is the most common condition for which that BoNT therapy with higher doses of the toxin may be required. In case of Botox, some patients may need over 400 units injected into the affected muscles to attain the satisfactory response. In Table 15.2, the safety information regarding BoNT therapy in cervical dystonia is presented along with the type and dose of the toxin. Only information from high quality and carefully crafted studies that compared the effects of the injected toxin with placebo are listed in this table. Since formulation of some toxins (for example Botox) has improved since 1997, the Table 15.2 includes only the data of the past 20 years.

The above- mentioned studies of botulinum toxin treatment in cervical dystonia (Table 15.2) indicate that the four FDA approved toxins are generally safe for this indication. However, treatment of cervical dystonia with botulinum toxins predisposes the patient to swallowing difficulty (dysphagia); swallowing difficulty is not an uncommon side effect and is more common when higher doses of the toxin are injected. Fortunately, most such cases are mild and self-limiting. Avoiding

Table 15.1 Double blind, placebo-controlled studies with BoNTs in children with spasticity

Study – Year published	Age range	Muscles involved by spasticity	Number of children	Type of toxin	Dose per session	Safety data, adverse effects (AEs)
Delgado et al. 2016	2–17 years	Calf muscles foot	241, 226 completed study	Dysport	10 and 15 units/kg	The treatment related AEs were all mild and transient and more in the placebo group (fever, weakness, fatigue, walking problem, incontinence – Each one case in toxin group No serious side effects.
Copeland et al. 2014	2.3–16 years	Calf and thigh muscles	41	Botox	12 units/kg not exceeding 400 units	Few patients reported as having serious side effects (nausea, vomiting, diarrhea, seizure) but not clear if toxin was the culprit. Same incidence in the placebo group
Koman et al. 2013	3–18 years	Upper limb muscles	73	Botox	Ranged between 1.4 to 12.5 units / kg	Adverse events were considered mild to moderate and statistically not different from the placebo group (29 reported in placebo and 25 in the Botox group).
Moore et al. 2008	2–8 year	Leg muscles	40	Dysport	30 units/kg	Adverse effects were mild and noted in both Dysport and placebo groups with similar frequency. No serious side effects were noted.
Bjorsen et al. 2013	Mean age: 5.4 years	Calf muscle	33	Botox	12 units/kg	Mild transient side effects – No difference between Botox (n = 30) and placebo(n = 26). Three children required ibuprofen for pain at injected site

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Table 15.1 (continued)

Study – Year published	Age range	Muscles involved by spasticity	Number of children	Type of toxin	Dose per session	Safety data, adverse effects (AEs)
Kawamura et al. 2007	Mean age: 6.2 years	Upper limb	39	Botox	Two groups 10 and 20 units/ kg	Considered mild: Week grasp, 3 in low dose and 2 in high dose groups. Fatigue 2 low dose 1 high dose. All fully recovered.
Mall et al. 2006	Mean age: 6 years	Thigh muscles	61	Dysport	30 units/ kg- maximum 1500 units/ session	Recorded as mild to moderate. Most frequent AE's were difficulty in swallowing, weakness and urinary incontinence. They were transient and slightly more frequent in the Dysport group.
Baker et al. 2002	Mean age: 5.2 years	Calf muscles	125	Dysport	10,20 & 30 units/kg	Falls (7), pain (8) and asthenia (4) were most common adverse effects with Dysport- most side effects were mild. No serious TRAE.
Ubhi et al. 2000	2–16 years	Leg muscles	40	Dysport	Two groups: 15 and 20 units/kg	Six adverse effects in the Dysport group (2 increased falls, post-injection calf pain; AEs were all mild and self- limiting.
Wissel et al. 1999	Mean age 10 years	Leg muscles	33	Botox	200	Treatment related side effects noted in 8 children- all considered mild, lasting 3–35 days, including unwillingness to walk (5), mild weakness (3), muscle soreness (2), local hematoma (1).

Table 15.2 Safety data and adverse effects of FDA approved BoNTs (Botox, Xeomin, Dysport and Myobloc) from high quality studies (placebo controlled, blinded) in cervical dystonia (past 20 years)

Authors and year published	Number of patients	Type of toxin	Dose (units)	Safety data and adverse effects (AEs)
Poewe et al. 2016	369	Dysport	500 (standard), 500 (liquid formulation)	No serious treatment-related AE (TRAE). Most common AEs were dysphagia and nasopharyngitis. Dysphagia was seen in 3.1% of patients who received the solution form and 7.1% of those who received the standard form. AEs were of mild and moderate severity
Yun et al. 2015	102	Botox	100	Neck weakness and dysphagia (8 in each toxin group); both mild and tolerable
		Dysport	250	
Evidente et al. 2013	219	Xeomin	Two groups	No serious treatment-related AEs. Incidence: 29% in 120u group and 38% in 240u group. Most AEs were mild to moderate. Dysphagia: 1–5% of the120 unit and 4–15% of the 240 unit group, respectively. No patient withdrew from the study.
			120	
			240	
Charles et al. 2012	214	Botox	360	AEs were reported in 59% of the Botox and 58% of the placebo group. Dysphagia was almost twice more common in Botox group compared to the placebo, rhinitis considerably higher in the botox group compared to placebo group. No serious adverse effects.
Comella et al. 2011	233	Xeomin	Two groups	No serious treatment-related AEs. Most SEs were mild to moderate.
			120	
			240	Dysphagia: 20% in 120 U, 16% in 240 U, 9% in placebo groups, respectively. Neck pain, dizziness, weakness, injection site pain considered severe AEs
Troung et al. 2010	216	Dysport	500	No treatment- related serious side effects. Dysphagia was the main AE noted in 5 of 55 patients (9%) in Dysport group, but none in placebo group. All AEs including dysphagia were of mild or moderate severity.
Pappert et al. 2007	111	Botox 55 pts	100	No serious treatment- related side effect. TRSE: 29% Botox. 51% Myobloc. Dysphagia, local pain, dry mouth. Dysphagia: Botox 14%, Myobloc18% (one case moderate intensity but did not require special care).
		Myobloc 56 pts	10,000	

(continued)

Table 15.2 (continued)

Authors and year published	Number of patients	Type of toxin	Dose (units)	Safety data and adverse effects (AEs)
Comella et al. 2005	140	Botox: 74 pts	250	No serious TRAE. Dysphagia: Botox 19%, Myobloc 48%
		Myobloc: 65 pts	10,000	Dry mouth: Botox 41%, Myo bloc 80% - all mild to moderate
Troung et al. 2005	80	Dysport	500	AE: Dysport 92%, placebo 79%
				Severe AEs: Dysphagia 16%, placebo 12%. No statistical difference. One patient in Dysport group had severe dysphagia
Wissel et al. 2001	68	Dysport	500	No serious TRAEs.
				Dysphagia:Dysport 3, placebo 1
				Dry mouth:Dysport 5, placebo2 neck weakness:
				Dysport 4, Placebo 0
Brashear et al. 1999	109	Myobloc	Two groups	Dysphagia: One in placebo group, 4 and 8 in low dose and high dose Dysport groups, respectively. None were severe.
			5000	
			10,000	
Lew et al. 1997	122	Myobloc	Three groups	Dyphagia: 0, 5, 3, 8 in placebo, low, medium and high dose groups, respectively (all mild).
			2500	
			5000	Dry mouth: 1,1,3,0, and pain (injection site) 2,6,10,10, respectively.
			10,000	
Brin et al. 1997	77	Myobloc	10,000	No serious TRAEs.
				Dysphagia: Toxin group: 11(6 moderate, 5 mild),
				Placebo group: 2
				Duration of moderate dysphagia:1–33 days

injection of large doses in the anterior neck muscles, knowledge of the injector of anatomy of neck muscles, and proper identification of the targeted muscle helps to avoid and minimize the potential development of this adverse effect. Employing electromyography (demonstrating the sound of muscle upon activation) or ultrasound technique (which visualizes the muscle) during the injection session also reduces the risk of experiencing dysphagia.

Long–Term Effects of Botulinum Toxins

The long-term effects of botulinum toxins have been the subject of several investigations shortly after introduction of botulinum toxin therapy to clinical medicine (1989). Investigators and clinicians were interested to know the answer to several questions:

1. Can the satisfactory response to the toxin be sustained after months and years of repeated treatment?

2. Is long-term therapy safe? Are there any unforeseen deleterious side effects that may develop with the long-term use?

In recent years, several studies have addressed the first question. Dr. Jankovic's group from Baylor College of Medicine looked at the long-term effects of botulinum toxin therapy on 111 patients with different dystonias [11] (a form movement disorder- see Chap. 11). Some patients were followed up to 20 years. They showed that patients' global response to injections improved after the last Botox injection compared to the first (3.57 over 3.18) and the mean duration of response after injection increased from the initial response of 16.33 weeks to 19.42 weeks with prolonged usage. In a large, multicenter study that included 1036 patients, researchers followed patients with cervical dystonia after repeated injections over a period of 3 years [12]. At the end of 3 years, 82.6% of the patients expressed satisfaction around the peak of the injected toxin's effect compared to slightly over half, at the beginning of therapy. In a Canadian study, Dr. Jog and his co-workers looked at the changes in quality of life in 1062 patients that had repeated Botox injections (for different indications) up to 22 years. The authors found that repeated Botox injections maintained initial improvement of quality of life over the long follow- up periods [13].

Regarding the long- term safety of botulinum toxin injections, the available data provides encouraging results. Dr. Santamato and his colleagues studied safety issues and adverse effects of high dose (up to 840 units) injections over two years in 20 patients who had developed limb spasticity after stroke. After 8 sets of injections, at two year follow-up point, no concerning safety issues were noted; specifically, there were no signs of significant spread or generalization [14]. Dr. Kenelly and collaborators [15] demonstrated that repeated injections of Botox into bladder wall maintained its efficacy over 4 years without development of any concerning safety issues (for bladder treatment with BoNTs see Chap. 8). Dr. Abaneh and his co-workers followed 32 patients with involuntary movements (blepharospasm and hemifacial spasm – see Chap. 11 of this book) for 14–17 years with repeated injections [16]. Although the mean injected dose of Botox was higher in the last year compared to the first injection, no safety issues were noted following the last set of injections. It has been shown by other researchers that in migraine, efficacy of Botox injections clearly improves after the second injection and no serious safety issues were noted in longterm treatment of chronic migraine (see Chap. 4 of this book on- migraine).

Conclusion

Botulinum toxin injected into the muscle has a potential to spread to remote muscles from the site of injection and cause serious side effects. The data from carefully crafted and placebo- controlled studies, however, indicate that the possibility of serious side effects from such toxin spread is remote and BoNT therapy is generally

safe. The efficacy of the injected botulinum toxin is maintained over years of follow-up; for some indications such as migraine, it clearly improves after repeated injections.

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