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Tremor and Other Hyperkinetic Movements

Reviews

History of Botulinum Toxin Treatment in Movement Disorders

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Abstract

Background: The frontiers of clinical medicine constantly expand as a result of the innovative efforts of visionary researchers and keen observations of seasoned clinicians. In medicine, rarely has a therapeutic agent been found efficacious in the management of so many symptoms and in such a relatively short time as botulinum toxin. One of the most notable contributions of botulinum toxin therapy in clinical medicine is in the field of movement disorders.

Methods: The English literature was searched using the Yale search engine including but not limited to PubMed and Ovid. The search includes articles from January 1 1980 to March 1 2016.

Results: A total of 2055 articles were identified. Of these, 132 met the criteria for this review.

Discussion: This historical review highlights early and seminal contributions that have introduced the application of botulinum toxins in the field of movement disorders and provides evidence-based contributions that have established botulinum toxin as an effective treatment for abnormal movements.

Keywords: Movement disorders, dystonia, botulinumtoxin, onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, rimabotulinum toxinB

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Introduction

Botulinum toxin, produced by *Clostridium botulinum* is a potent toxin capable of rendering therapeutic effects based on its specific synaptic physiology. While playing at a funeral on December 14, 1897, a group of 34 Belgian musicians consumed smoked ham and developed visual and gastrointestinal symptoms characteristic of botulism; three of the 34 died. The remaining ham and some of the deceased organs were sent to Emile van Ermengem, professor of bacteriology at the University of Ghent.[1] He found the responsible agent and named it *Bacillus botulinum* after the Latin word of botulus for sausage. In early 20th century, the word *Clostridium* (spindle shape) replaced the word *Bacillus* (*Clostridium botulinum*). During the latter years of World War II, Carl Lamanna and Edward Schantz isolated and purified the toxin in the US Army facility of Fort Dietrich, Maryland. In 1946, Schantz produced a large volume of the purified toxin and continued his research at the University of Wisconsin with Eric Johnson and other co-workers. In 1965, Drachman[2] demonstrated paralysis and atrophy of chick's muscles after botulinum toxin injection, a finding that encouraged Allan Scott, an ophthalmologist, to investigate it further for treatment of strabismus. Dr. Scott's research during the 1960s and 1970s led to Food and Drug Administration (FDA) approval for conducting human research using the toxin for treatment of strabismus (1979). Ultimately, the FDA approved the use of Schantz toxin (then called oculinum) for treatment of strabismus, blepharospasm, and hemifacial spasm (HFS) in 1989. Over the next 26 years, research exploded in this area; different toxins were developed and botulinum toxin was approved for several other movement and autonomic disorders including cervical dystonia (CD), hyperactive bladder, sialorrhea, hyperhidrosis, migraine, and spasticity.

Botulinum toxin has eight major serotypes designated as A, B, C, D, E, F, G, and H. Only type A and B are used in clinical practice because of their longer period of action. The molecular weight of 150 kDa for the core toxin plus surrounding proteins (ranging from 500 to 900 kDa) does not allow absorption of the toxin complex through the skin. The toxin's core consists of a light chain (50 kDa) and a heavy chain (100 kDa) attached together by a disulfide bond. After

intramuscular injection, tissue protease nicks the toxin and detaches the toxin molecule from the protein complex within minutes.[3] The heavy chain of the toxin attaches the toxin to the outer surface of the presynaptic membrane at specific polysialogangioside receptors. The toxin then enters the vesicles by endocytosis. Once inside the vesicle, the low pH helps the toxin to enter the lipid layer of the vesicle wall. The heavy chain translocates the light chain from the vesicle into the cytosol and it then attaches to the target SNARE proteins (soluble N-ethylmaleimide sensitive fusion protein attachment receptor proteins).[4] These proteins are specific peptides that constitute the main machinery of vesicle fusion into the synaptic membrane, vesicle rupture, and release of the neurotransmitter.[5] The SNARE protein SNAP 25 was first identified by Yale investigators as the site of attachment of type A toxin's light chain.[6] The light chain, a zinc-activated peptidase, then catalyzes the peptide structure of SNARE protein preventing vesicle fusion and rupture. For the type B toxin, the SNARE protein is attached to the surface of the vesicle itself (VAMP, vesicle attached membrane protein).

Currently three type A and one type B toxin are approved by the FDA for clinical use in the United States. The type A toxins are Botox (onabotulinumtoxinA) produced by Allergan Inc., Xeomin (incobotulinumtoxinA) from Merz Pharma, and Dysport (abobotulinumtoxinA) from Ipsen. The type B toxin, Myobloc (rimabotulinum toxin) is produced by Solstice/US World Meds. In comparator clinical trials sometimes unit comparisons are used (1 onabotulinum toxin unit=1 incobotulinum toxin unit=3 abobotulinum toxin units=40–50 units of rimabotulinum toxin. However, there is significant individual variability and weakness does not necessarily predict the desired clinical effect.

There are other differences among these toxins. For example, incobotulinumtoxinA has less immunogenicity than other toxins and does not need to be refrigerated (recommended by the manufacturer for the other two type A and the type B toxins). RimaboutlinumtoxinA comes as a prepared solution, whereas the other three toxins come as powders in a vial and require dilution with preservative-free saline before injection.

Search method

For this historical review, the author searched the English literature using the Yale search engine including but not limited to PubMed and Ovid. The search includes articles from January 1 1980 to March 1 2016. The search terms consisted of botulinum toxin or botulinum neurotoxin plus the following terms: history, movement disorder, dystonia, blepharospasm, laryngeal dystonia, task-specific dystonia, HFS, tremor, chorea, tics, Tourette syndrome. Additionally, botulinum toxin plus three uncommon movement disorders were also searched: spinal myoclonus, painful/painless legs moving toes, and painful/painless arm moving fingers.

The search identified a total of 2,055 articles published from January 1 1980 to March 1 2016, 132 of which met the criteria defined for this review. The criteria for selection consisted of 1) manuscripts that described the history of botulinum toxin discovery and predicted its clinical usefulness; 2) manuscripts that provided early descriptions of molecular structure and mechanism of function; 3) manuscripts that pioneered application of botulinum toxins in movement disorders; 4) review articles of historical significance that provided information regarding the development of new applications or clinical extension of old applications.

Results

A brief historical note

Justinus Kerner (1786–1862), a German physician, is credited as being the first to recognize the potential of botulinum toxins for treatment of hyperkinetic movement disorders and conditions of autonomic dysfunction. Kerner's observations and contributions are described in a series of recently published articles by Erbguth and Naumann.[7–9] In brief, Kerner, who witnessed several outbreaks of botulism after consumption of smoked sausage, described in detail symptoms of 76 and 155 patients in two seminal articles published in 1820 and 1822. He believed a fat poison, most likely biologic and not environmental, was responsible for the patients' illness. Considering the patients' symptoms of weakness, dry mouth, and reduction of body secretions, Kerner predicted that the sausage/fat toxin had a potential to alleviate symptoms of muscle hyperactivity or those symptoms caused by "hyperexcitabiliy of the sympathetic nervous system."

History of botulinum toxin treatment in common movement disorders

Dystonia. Dystonia is a neurologic syndrome characterized by involuntary sustained, patterned, and often repetitive muscle contractions of opposing muscles causing twisting or spasmodic movements or abnormal postures.[10] Treatment of dystonic symptoms with botulinum toxins is now a major area of medical practice.

Blepharospasm. Blepharospasm is a focal dystonia of orbicularis oculi muscles that leads to frequent blinks and, in severe cases, forced closure of the eyes. In one study, the average age of onset of essential blepharospasm was between the fifth and sixth decades, with a female to male ratio of 2.8:1.[11] Blepharospasm responds well to anticholinergic medications, but a satisfactory response may require high doses (exceeding 30 mg/day for trihexyphenidyl), resulting in memory loss and confusion which is poorly tolerated by elderly people.

In 1984, Frueh et al.[12] reported a positive response lasting for 10 weeks in "most of the 22 patients with blepharospasm" who were injected with botulinum toxin A (then called oculinum). In the following year, Scott et al.[13] described 39 patients with blepharospasm who were followed for up to 170 days with repeated periocular oculinum injections; all responded. In the same year, a group from Columbia University in New York[14] supported Scott's observation via their positive findings in a small blinded study of five patients. Another small, blinded study from Baylor College of medicine on 12 patients (in 1987) demonstrated similar positive results.[15] Over the next few years several large open clinical observations reported excellent results with Botox in the treatment of blepharospasm. Professor Fahn quotes a personal communication with Dr. Scott in 1990 in which Dr. Scott described very good results with treatment of nearly 2,000 patients.[16] In 1989, based on these vast

observations, the FDA approved treatment of blepharospasm with onabotulinum toxin A despite the lack of class I or II blinded studies at that time.

In the most recent review of botulinum toxin treatment of blepharospasm, Karp and Alter[17] define botulinum toxin as the first line of treatment for blepharospasm with an efficacy rate of over 90% based on the accumulative literature. Botulinum toxins are effective in both essential and secondary blepharospasm. Experience of up to 26 years has demonstrated continued efficacy with repeated injections, although a small increase in the dose may be necessary over time to maintain the same level of efficacy.[17,18] The most recent guidelines of American Academy of Neurology[19] assigns level B evidence (probably effective) to incobotulinumtoxinA and onabotulinumtoxinA toxins and a level C evidence (possibly effective) to abobotulinumtoxinA for treatment of blepharospasm. It states, however, that in view of most experts in the field of movement disorders, botulinum toxins are considered the first line of treatment for blepharospasm.

Hemifacial spasm. HFS is not a dystonia but it is placed here due to its semeiologic and regional similarities to blepharospasm. Babinski coined the term hemifacial spasm (hemispasme facial) in 1905 but the condition had been described earlier by others (Schultze 1875, Gowers 1885).[20] A prevalence of 11 in 100,000 had been reported for HFS, with female to male predominance of 2:1.[21,22] HFS involves one side of the face with focus around the eye and, in many patients, there is also involvement of the ipsilateral facial muscles close to the corner of the mouth. In most cases, the cause is an anomalous and ectatic blood vessel that impinges upon the facial nerve as it exits from the brain stem. Treatment with anticonvulsants and clonazepam can be partially effective.[17] Neurovascular decompression is effective in most cases, but in some cases it can cause serious morbidity.

The efficacy of type A toxin (oculinum/Botox) in HFS was first reported in three patients in 1984,[12] and subsequently in another open observation of 15 patients in 1985.[23] Subsequent observations in a large number of open studies with a sizeable number of patients strongly supported the efficacy of botulinum toxins in HFS. The FDA approved onabotulinumA for treatment of HFS in 1989. Recently, Hallett et al.[24] have evaluated the efficacy of botulinum toxins in movement disorders using the efficacy criteria of the American Academy of Neurology.[25,26] The level of efficacy for botulinum toxin treatment in HFS was designated as B, probably effective, based on two double-blind, class II studies.[27,28] The data were available only for onabotulinumtoxinA and abobotulinumtoxinA. OnabotulinumtoxinA was given a level B efficacy based on two level II studies, and abobotulinumtoxinA a level C efficacy, possibly effective, based on one level II study. However, these class C and B studies had several limitations, including a lack of concealment, a small number of participants, a single blind design, and a high rate of patient dropouts. It is currently believed that botulinum toxin treatment is the treatment of first choice in HFS. Long-term data have shown that 76–100% of patients demonstrate at least 75% improvement of their symptoms after botulinum treatment.[17]

Cervical dystonia. CD is the most common form of focal dystonia with a prevalence of five out of 100,000 cited in some studies.[29] In a recent large study, the mean age of onset was 49 years and 74% of the patients were female.[30] The percentage of different forms of CD was as follows: torticollis (rotational posture) 47.5%, laterocollis (lateral tilt) 38.9%, antecollis (anterior bent) 5.7%, and retrocollis (posterior bent) 5.3%. Limitation of head rotation, usually one side more than the other, is one of the hallmarks of torticollis. Torticollis is sometimes associated with head jerks that are intensified when the head is rotated toward the direction of limitation (named by some myoclonic dystonia). Before introduction of botulinum toxins, anticholinergic drugs such as trihexyphenidyl (Artane) and benztropine were the most effective treatment. However, their utility is limited, particularly in older individuals because of frequent onset of memory loss, delusions, and visual hallucinations. Clonazepam is effective in reducing the myoclonic head jerks in CD.

In 1985 and 1986, Tsui and co-workers[31,32] first reported on the efficacy of botulinum toxin A in CD. Their first article, an open study, demonstrated an improved range of head movement and neck pain after Botox injection into the neck muscles of 12 patients. The second article, a double-blind, placebo-controlled trial of 21 patients, showed that onabotulinumtoxinA treatment produced subjective and objective improvement as well as pain relief in 63%, 53%, and 88% of the patients, respectively. For the placebo group, the same improvement figures were 35%, 15%, and 24%.

Over the next 10 years a number of class II and class III double-blind studies suggested the efficacy of botulinum toxins in CD. In one such class II study, Greene et al.[33] demonstrated further improvement of CD symptoms after second injection. The initial rate of 67% rose to 74% after a second treatment during the extended open phase.

The first class I study of botulinum toxin treatment of CD was reported by Lew et al.[34] for type B toxin in 1997. The investigators tested 122 patients in a double-blind, placebo-controlled protocol. The type B injected group received two total doses of 2500 and 5000 units. The primary outcome at 4 weeks was improvement in the Toronto Western Spasmodic Torticollis Rating Scale. There was a significant difference between the two groups in favor of botulinum toxin B.

Bledso and Comella's[35] recent review identified a total of eight class I, double-blind, placebo-controlled, multicenter studies assessing the efficacy of different botulinum toxins in CD. The authors also included five additional comparator studies in this report. To date, there is one class I, placebo-controlled study for onabotulinumtoxinA, three placebo-controlled and two comparator studies (one with trihexiphenidyl and one with Botox) for abobotulinumtoxinA, one placebo-controlled and one comparator study (with onabotulinumtoxinA) for incobotulinumtoxinA, and three placebo-controlled and two comparator studies (with onabotulinumtoxinA) for rimabotulinumtoxinB. The results have consistently shown efficacy of all four toxins in CD. On the basis of these data, a group of experts designated a level A efficacy (established, effective) for all four botulinum toxins (three type A and one type B) for CD treatment.[23] The FDA approved rimabotulinumtoxinB and onabotulinumtoxinA in the year 2000 and

abobotulinumtoxinA and incobotulinumtoxinA in 2009 for CD treatment in the United States.

Task-specific dystonia. Task-specific dystonias are a group of focal dystonias in which dystonic posturing and contractions of certain muscles occur during specific acts and lead to motor dysfunction. The existence of task-specific dystonia was recognized by astute clinicians in the 19th century. Charles Bell (1830) described cases of dystonic writer's cramp and Gowers (late 1800s) reported cases of musicians' dystonia.[36] Cohen et al.[37] studied electromyography (EMG)-guided injection of onabotulinumtoxinA in 19 patients with TSD, 12 of whom had dystonic writer's cramp and five who had musician's dystonia (piano and guitar players). Sixteen of the 19 patients showed improvement of function. Their finding is consistent with 60–70% improvement that was found in three small, class II blinded studies with onabotulinumtoxinA conducted a few years later[38–40] and a more recent double-blind class I study using abobotulinumtoxinA for writer's cramp/dystonia.[41] Hallett et al.[42] provided a comprehensive review of botulinum toxin treatment in focal hand dystonia, including that of musicians and dystonic writer's cramp. Many patients with musician's dystonia also report some improvement of performance after treatment, but most subjects are not able to achieve their previous/initial level of precision. Hand weakness is a common side effect but is not often disabling. Lungu et al.[43] reported on 10 years or longer follow-up of 20 patients with dystonic writer's and musician's cramp. The patients tolerated the repeated injections well. The continued response with repeated injections over such a long time reflected low immunogenicity.

Laryngeal dystonia (spasmodic dysphonia). Laryngeal dystonia is a form of task-specific dystonia. The appearance of the vocal cords is normal, but vocal cords either over-adduct or over-abduct during talking. In the adductor type, the patient's voice is strained and strangled, whereas the abductor type produces a breathy and whispering voice.[44] Overactivity of the thyroarytenoid muscle is responsible for the more common adductor type, whereas contractions of the posterior cricoarytenoid muscle causes abductor laryngeal dystonia. Andrew Blitzer, an oto-laryngologist, was first to inject botulinum toxin A into the vocal cord muscles for treatment of laryngeal dystonia in 1984.[45] Since then, over 50 publications reported positive results in this area. Blitzer et al.[46] have recently reported their experience over a period of 30 years with 901 patients suffering from laryngeal dystonia. The mean age of the patients was 39 years: 63% were female, 82% had adductor, and 17% had the abductor type of laryngeal dystonia. Over 90% of the patients responded to treatment with the level of voice improvement reported by the patients as 70.3% for adductor and 55% for abductor dystonia. Bilateral injection with approximately 1 unit (in the case of onabotulinumtoxinA) is recommended for adductor dystonia. For unilateral injection, the required dose is more (up to 3.75 units). Injections are through a hollow EMG needle after EMG-guided identification of the muscle. Despite the lack of blinded studies, botulinum toxin injection into the vocal cord muscles is now considered the first approach for management of laryngeal dystonia because of the high rate of success. A low and breathy voice for days after injection is the most common side effect; however, patients in general tolerate this inconvenience for experiencing a remarkable voice improvement that can last for 3–6 months.

Tremor. Tremor is a rhythmic, oscillatory movement that is caused by involuntary contraction of the agonist/antagonist muscles. It can be classified into rest and action tremor. Action tremor includes four types: postural, kinetic, task-specific, and isometric tremor. Lotia and Jankovic[47] have recently reviewed the role of botulinum toxins in the management of different tremors.

Essential tremor

In 1991, Jankovic and Schwartz[48] first reported the effect of onabtulinumtoxin A in 34 patients with essential tremor in an open observation. Tremor improved in 67% of the patients, but 60% demonstrated hand weakness following injection into arm flexors and extensors. To date, two double-blind placebo-controlled studies have been conducted in this area. Both studies have used a fixed-dose injection design. The first study investigated 25 patients in 1996.[49] The patients were injected with a total of 50 units of onabotulinumtoxinA into two wrist flexors and two wrist extensors. If there was no appreciable response within 4 weeks, a second injection of 100 units into those muscles was employed. Although there was no statistically significant difference between the toxin and placebo groups, the toxin group showed subjective improvement of tremor with 75% of the patients demonstrating a two-grade improvement in the tremor scale. Between 42% and 50% of the patients developed hand weakness but it was non-disabling. The second study[50] was multicenter, fixed dose, and parallel design, and was conducted on 133 patients. Two groups of low dose (50 units) and high dose (100 units) of onabotulinumtoxinA were compared with placebo. There was a statistically significant difference in terms of tremor improvement (kinetic at 6 weeks and postural at 6, 12, and 16 weeks) that was more prominent in the high-dose group. There was dose-dependent hand weakness in a majority of the patients. Both blinded studies considered the fixed-dose design a weakness of the protocol and recommended a customized approach for future trials.

Rest tremor

Rest tremor is the hallmark of Parkinson's disease (PD). A number of patients with PD also demonstrate postural tremor. In an open study, Pullman et al.[51] first reported a mean of 13% improvement of parkinsonian rest tremor after onabotulinumtoxinA injection into the forearm muscles. Overall, 35.7% of the patients responded to the treatment with onabotulinumtoxinA. In the same year, Henderson et al.[52] compared the effect of 25 and 50 units of onabotulinumtoxinA with placebo in 17 PD patients in a single blind study. In the botulinum toxin group, 40% showed improvement of the rest tremor and 57% demonstrated improvement of postural tremor, twice that of the placebo group. The authors noted the development of hand weakness in nine of 17 patients and commented on the need for better-designed studies to avoid hand weakness. Recently, the preliminary results of a

double-blind placebo-controlled study of incobotulinum toxin A in PD tremor was published by the Yale group in an abstract form.[53] In this customized double-blind, crossover study, 100–120 units of incobotulinumtoxinA was injected into eight to 10 different forearm and hand muscles of 30 patients and the results were compared with a placebo over 14 weeks of observation. Both tremor subsets of the Unified Parkinson's Disease Rating Scale (UPDRS) and National Institute of Health (NIH) tremor scales improved significantly (2 grades or more) in the incobotulinumtoxinA ($p=0.001$). Marked improvement in "patient global impression of change" was reported by eight patients in the toxin group in contrast to none among patients in the placebo group ($p=0.007$). Moderate to severe weakness of the hand was noted in two patients (6%) in the incotoxin group and one patient (3%) in the saline group.

There are positive case observations on the use of botulinum toxins in other types of tremors such as essential voice tremor, essential head tremor, palatal tremor and primary hand tremor; These await confirmation by blinded studies.

Tics and Tourette syndrome

Tics are sudden, rapid, recurrent, non-rhythmic movements (motor tics) or sounds (phonic tics).[54] Motor tics can be clonic, dystonic, or tonic and manifest with simple or complex symptomatology. Complex tics are often seen in Tourette syndrome, which also includes vocalization and behavioral problems (obsessive compulsive disorder, attention deficit). Dopamine-blocking agents (fluphenazine and aripiprazole), α-2-agonists such as clonidie and guanfacine and/or dopamine-depleting drugs such as tetrabenazine may improve motor and vocal tics. Recalcitrant tics may respond to deep brain stimulation,[55] yet still some fail to respond to both medical and surgical approaches.

Jankovic[56] first reported moderate improvement of blinking and dystonic tics in 10 patients after intramuscular onabotulinumtoxinA administration in 1994. Subsequently, in the year 2000, he and his co-workers published[57] a case series of 35 patients in whom the same toxin was injected for treatment of motor tics in different facial and cervical muscles including the vocal cords. The improvement rate was 78% on a global rating scale and 84% for premonitory sensation (urge). In another open study,[58] investigators evaluated the efficacy of bilateral injection of onabotulinumtoxinA (2.5 units) into the vocal cords of 22 patients with vocal tics. Using Hopkins Vocal Tic Scale, 93% of the patients improved and another 50% demonstrated improvement of the "interference in life scale." Finally, Marras et al.[59] conducted a double-blind, placebo-controlled, crossover study in 18 patients with motor tics of the facial, neck, and shoulder muscles. A statistically significant improvement compared with placebo was noted in 39% of the patients with motor tics. A low statistical power because of the small number of patients may have accounted for non-significant values obtained for the changes in quality of life in this study. Although limited, the results of the aforementioned studies indicate that botulinum toxins can improve focal motor and phonic tics[46] and necessitate larger clinical trials in this area to be conducted.

History of botulinum toxin treatment in uncommon movement disorders

Two uncommon movement disorders in which botulinum toxin data are available are selected for this review. The rationale for selecting these two is twofold: 1) the literature on others (myokymia, paretic facial contracture, chin tremor, etc.) is limited to one or more single case reports; 2) these two selected movement disorders are often more disabling than others.

Spinal myoclonus

Spinal myoclonus (spinal segmental myoclonus) is caused by a lesion or dysfunction of one or more segment(s) of the spinal cord. It can result from diverse causes including tumor, trauma, infection, and demyelination.[60] Spinal myoclonus is often rhythmic, involving one or both legs. In some cases, it is associated with significant leg pain and discomfort. Treatment of spinal myoclonus is difficult and often unsuccessful. Clonazepam and valproic acid can be partially effective. With clonazepam, relief may require doses of up to 6 mg/day. Leviteracetam 500–1000 mg/day has helped a limited number of patients.

Polo and Jabbari[61] first reported marked improvement of painful spinal myoclonus after intramuscular administration of onabotulinumtoxinA. The patient was a 16-year-old female with Scimitar syndrome (vascular cardiopulmonary anomaly) who suffered from sudden paraplegia secondary to an acute mid-thoracic spinal cord infarct. The right leg remained paralyzed and atrophic but the left leg gradually regained near full strength. After 4 years, however, she developed rhythmic and painful rhythmic involuntary movements of the left rectus and vastus muscles. Injection of 280 units of onabotulinumtoxinA into the left quadriceps (rectus 100, V. medialis 90, and V. lateralis 90 units) markedly reduced the movements and stopped the pain. The effect lasted 5 months and was duplicated after a second injection. In a subsequent report, a case of stimulus sensitive spinal myoclonus was reported who responded well to intramuscular administration of botulinumtoxin A.[62] Another case report described a 26-year-old female with segmental C1–C3 spinal myoclonus in whom injection of botulinumtoxin A into the infrahyoid and cervical paraspinal muscles stopped the movements. The effect lasted for 5 months.[63] In a recent review article on propriospinal myoclonus, the authors reported 20 patients from the world literature who had responded to botulinum toxin treatment.[64]

Painful/painless legs, moving toes and painful/painless hands, moving fingers

This entity was first described by Spillane et al.[65] in 1971 and designated as "painful leg moving toes". Other similar entities, but less common, include painless leg moving toes and painful or painless hand moving fingers.[66] A significant majority of these patients have a history of damage to the peripheral nervous system (peripheral nerve, plexus, root) preceding the onset of involuntary limb movements/pain by months or years. However, there is evidence for central mechanisms

Table 1. **The Historical Timelines on Emergence of Botulinum Toxin as a Therapeutic Agent**

1817–1822	Observations and seminal writings of Justinus Kerner on symptoms of botulism outbreaks in Germany
1897	Emile Van Ermengem finds the responsible agent for botulism and calls it bacillus botulinum
1924	The name clostridium botulinum was introduced by Ida Bengton
1942–1946	Carl Lamanna and Edward Schantz purify the toxin and prepare it in crystalline form
1946	Schantz produces a large amount of this toxin and makes it available for clinical research
1964–1966	Drachman demonstrates the paralytic effects of botulinum toxin and its physiology in an animal model (chicks embryos)
Late 1960s to early 1970s	Allen Scott an ophthalmologist, further studies the paralytic effects of the botulinum toxin in primates
1973	Scott publishes the first paper on weakening of extraocular muscles of monkeys
1979	FDA approves conducting research with botulinum toxin in human subject
1989	FDA Approves, Allergan's Oculinum (later called Botox, onabotulinum toxin A) for treatment of strabismus, blepharospasm and hemifacial spasm

Table 2. **First Randomized, Double-blind, Placebo-controlled Studies with Botulinum Toxins in Movement Disorders**

Movement Disorder	Authors	Year	Type of Toxin
Cervical dystonia	Tsui et al.[31]	1986	OnabotulinumtoxinA
Blepharospasm	Jankovic and Orman[15]	1987	OnabotulinumtoxinA
Hemifacial spasm	Yoshimura et al.[38]	1992	OnabotulinumtoxinA
Task-specific dystonia	Cole et al.[40]	1995	OnabotulinumtoxinA
Essential tremor	Jankovic and Schwartz[48]	1996	OnabotulinumtoxinA
Simple motor tics	Marras et al.[59]	2001	OnabotulinumtoxinA
Rest tremor	Shivam et al.[53]	2016	IncobotulinumtoxinA

based on electrophysiology and the clinical course; for example, similar movements may develop in the contralateral leg.[67,68] Movements are semi-rhythmic and irregular and EMG often shows periodic discharges similar to myokymia.[67] In some patients, the limb pain is severe and disabling. Pharmacological treatment is often not helpful.[68,69]

In 2007, Singer and Papapetropoulos[70] first reported 80% improvement of bilateral involuntary finger movements with onabotulinumtoxinA injection into flexor digitorum superfecialis (12.5 units) in a 20-year-old female who had bilateral painless hand, moving fingers. In 2008, Eisa et al.[71] first described marked improvement of pain and involuntary toe movements in two patients with painful legs, moving toes. OnabotulinumtoxinA was injected under EMG guidance into the flexor digitorum brevis and gastrocnemius muscles bilaterally in one patient (total 100 units) and in the flexor digitorum longus (total 50 units) in the other patient. In subsequent years, a similar experience with botulinum toxins in painless leg moving toes was reported by others in regard to both movement and pain improvement.[72]

Owing to the infrequency of spinal myoclonus and painful/painless limb disorders, it is unlikely that the efficacy of botulinum toxins can be studied in these conditions under a randomized, blinded, placebo-controlled protocol that includes a sizeable number of patients.

Table 1 demonstrates the time lines for development of botulinum toxin as a therapeutic agent. Table 2 shows the first double-blind studies reported for botulinum toxin treatment in movement disorders.

Conclusion

This historical review identifies early contributions that were essential for introduction and establishment of botulinum toxins for treatment of movement disorders. Botulinum toxins are now established as the first line of treatment for HFS, blepharospasm, and laryngeal dystonia and are considered a major treatment modality for limb dystonias, including the task-specific dystonias. Early data on essential tremor and Parkinson tremor and on tics are also encouraging and reflect a potential for future application.

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