Botulinum neurotoxin for the treatment of movement disorders

CPD

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Background
Botulinum neurotoxin (BoNT) is an exotoxin that causes neuromuscular weakness. BoNT serotypes A and B have been used for decades for the safe and effective treatment of various movement disorders, including some forms of focal dystonia. These conditions, such as cervical dystonia, hemifacial spasm, blepharospasm and spasmodic dysphonia, can have a substantial impact on patients' quality of life, but are often under-recognised.

Objective
The aim of this article is to describe the usefulness of BoNT for the treatment of movement disorders, including a description of its mechanism of action, mode of administration, indications and evidence of benefit.

Discussion
General practitioners have a vital role in the identification of patients with potentially treatable movement disorders such as cervical dystonia. Treatment with BoNT can improve patients' function, reduce pain and improve workforce participation. Patients require ongoing periodic injections by a trained neurologist to obtain long-term benefits with minimal side effects.

BOTULINUM NEUROTOXIN (BoNT) has become a common first-line treatment in a variety of conditions, such as focal dystonias, to reduce pain and improve quality of life and function.[1] Botulism was first described in the 18th century when it was linked to the consumption of improperly preserved sausages, which led to an acute fatal illness following a clinical syndrome characterised by neuromuscular weakness and anticholingeric symptoms. The Latin word *botulus*, meaning sausage, was later used to name the causative organism, *Clostridium botulinum*.[2]

Mechanism of action of BoNT

Isolation of the exotoxin produced by anaerobic *C. botulinum* serotypes A and B has led to its safe therapeutic use. When injected into muscle, BoNT acts by inhibiting the release of acetylcholine from the presynaptic terminals at the neuromuscular junction (NMJ). This is achieved by interfering with the normal process of vesicle–plasma membrane fusion.[3] There are also suggested clinical effects beyond the local neuroparalysis, including plasticity of central nervous system circuits due to blockade of sensory afferent gamma units of muscle spindles.[4]

BoNT administration

Recovery of the NMJ, approximately three months post-injection of BoNT, leads to recurrence of symptoms. BoNT is frequently injected in combination with electromyography (EMG) or ultrasonography to target appropriate muscles. The use of EMG-guided BoNT injection can improve treatment outcomes in dystonia.[1] EMG improves the accuracy of targeting dystonic muscles, as there is a significant amount of subcutaneous tissue and several muscle layers in the neck. However, the relatively small improvement is controversial in some conditions, given the additional time taken to perform EMG and the associated discomfort and cost.[1] For this reason, EMG is used less often in conditions such as blepharospasm and hemifacial spasm, where treatment can be achieved effectively because of the relatively superficial location of target muscles.

Currently, formulations of BoNT type A available under the Pharmaceutical Benefits Scheme (PBS) are onabotulinum toxin A (Botox), abobotulinum toxin A (Dysport) and incobotulinum toxin A (Xeomin). The dosage is not equivalent between agents.[3] Although rare, the formation of antibodies may require use of type B BoNT, which is not available on the PBS.

Identification of patients who may benefit from treatment with BoNT

BoNT is commonly used for various neurological conditions including chronic migraine, spasticity and movement disorders. This article will discuss indications for movement disorders. Treatment of spasticity has been recently

discussed in the Australian context elsewhere.[5] Specific types of movement disorders that benefit from BoNT include forms of dystonia. This disorder is characterised by involuntary sustained or intermittent muscle contractions that result in disabling and painful, often repetitive, abnormal movements or postures.[6] It is a highly disabling condition that leads to serious functional and social impairments. Early retirement, depression and diminished health-related quality of life occur at rates comparable to conditions such as multiple sclerosis and Parkinson's disease.[7] Recognising dystonic movements requires detailed observation of patterned muscle contractions producing abnormal movement, which at times can be tremulous in nature. Tips for identifying dystonia include:

- examining the patient directly from the front
- observing any asymmetrical movements or posture
- evaluating how movement in certain directions may exaggerate or lessen the dystonic movement; classically, there is a quieting or 'null point' of dystonia when the affected area is positioned to the area of pull
- evaluating for features of 'sensory trick'; dystonic movements are often diminished by tactile or proprioceptive input (eg the patient touches the involved dystonic body part to reduce movement)[8]
- identifying increased likelihood of diagnosis given comorbid disease (eg Parkinson's disease).

Focal dystonias can be isolated to a specific region, vary in phenotype or overlap with each other (eg cervical dystonia with blepharospasm). Patients often dismiss or mask their impairments for prolonged periods or may have been incorrectly diagnosed (Cases 1, 2). In an Australian cohort of patients with cervical dystonia, the average time to diagnosis was 6.8 years.[9] Delays in diagnosis are associated with reduced quality of life and social embarrassment of the condition.[9] General practitioners (GPs) are essential in early identification and referral of patients.

CASE 1

A retired male public servant aged 62 years had been experiencing four years of head-shaking tremor. He also had an irregular and jerky tremor in his upper limbs. As the condition progressed, other people had commented on the tremor and neck posture. The frequent comments contributed to low self-esteem and depression. He had been treated with medication for Parkinson's disease to target his limb tremor, and musculoskeletal neck pain was thought to be the cause of poor neck posture. When reviewed for a second opinion, he was diagnosed with cervical dystonia and dystonic tremor. On examination, there was a left torticollis (head rotation) with left head tremor. He was unaware of his sensory trick of frequently touching the left side of his neck to attenuate the tremor. There were no extrapyramidal features such as bradykinesia or cogwheel rigidity. He was treated with BoNT at three-monthly intervals for cervical dystonia. His medications for Parkinson's disease were gradually ceased. Ultimately, there was reduced neck pain and cervical tremor, resulting in an improved quality of life.

CASE 2

A female interior designer aged 56 years was referred with an 18-month history of blepharospasm. Initially, she had been treated for dry eyes with lubricating eye drops. As the condition progressed, it affected her ability to drive and work because the frequency of eye closure was impairing her functional vision. She was commenced on a three-monthly treatment of BoNT for blepharospasm. She had mild transient ptosis during the first week post-treatment. On subsequent review at three months, she reported improved functional vision, and was able to return to work and drive. Ptosis post-treatment did not recur with a reduction in dose with subsequent treatments.

Indications and evidence for BoNT

Although BoNT is a relatively expensive treatment, there is evidence to support its use in a variety of conditions to improve function and quality of life and reduce pain symptoms.[1] BoNT is funded through the PBS for use in some focal dystonias including cervical dystonia, blepharospasm, hemifacial spasm and oral mandibular dystonias. Evidence from observational studies suggests that this may translate to improved return-to-work outcomes.[7] Specific indications for BoNT in movement disorders with a supportive evidence base include the following conditions.

Cervical dystonia

This is the most common form of focal dystonia, with an estimated prevalence of five per 100,000 and a mean age of onset of 49 years; 74% of patients are female.[3] Potential differential diagnoses include musculoskeletal neck pain or trochlear nerve palsy with compensatory head tilt. Patients most commonly have torticollis, with possible additionally lateral head tilt (laterocollis). There may be a head bent forward posture (anterocollis) or head back posture (retrocollis). Most patients have associated neck pain. A Cochrane systematic review of randomised control trials (RCTs) supports, with moderate certainty, that BoNT is well tolerated and produces a clinically significant reduction of functional impairment and pain.[10] There is also evidence that BoNT in conditions such as cervical dystonia favourably alters the natural course of the disease.[1]

Blepharospasm

Blepharospasm is a focal dystonia of the orbicularis oculi muscles that results in repetitive eye closure. Age of onset is often in the fifth and sixth decade, with women approximately three times more affected than men. It can be idiopathic and is rarely associated with brain stem pathology. Potential differential diagnoses in the elderly include eyelid-opening apraxia associated with conditions such as progressive

supranuclear palsy. Other mimics in a young patient include Tourette syndrome, psychogenic blinking or dry eyes. Supporting evidence for the use of BoNT includes RCTs suggesting probable efficacy, with international guidelines supporting its long-term effectiveness and improved quality-of-life outcome measures.[3]

Hemifacial spasm

A peripheral nerve disorder, rather than dystonia, hemifacial spasm is characterised by intermittent muscle contraction of half of the face. The condition, which is twice as common in women, usually starts with the orbicularis oculi muscle and subsequently spreads to the remainder of the facial muscles of the unilateral side. It can often be mistaken for facial tics or, less commonly, focal seizures. The aetiology is most commonly related to a small anomalous vessel causing compression against the facial nerve as it emerges from the brainstem. BoNT is regarded as a first-line therapy for the condition; however, because of the lack of blinded RCTs, international guidelines suggest probable effectiveness of the treatment.[3]

Spasmodic dysphonia

Spasmodic dysphonia is a dystonia of the laryngeal muscles. Dystonia in the thyroarythenoid muscles results in over-adduction of the vocal cords. As a result, patients present with a strained, tremulous, harsh voice with inappropriate pitch and pitch breaks. The less common abductor type is caused by dystonia of the posterior cricothyroid muscles, which results in a hypophonic whispering voice due to abduction of the vocal cords. Other clinical features may include dystonic cough, intermittent stridor, uncoordinated breathing and paroxysmal hiccups. Evidence for treatment of the condition is a single, small-sized, blinded RCT of efficacy, with international guidelines suggesting probable efficacy.[3] Treatment is not PBS-funded.

Oral mandibular dystonias

These conditions include involuntary movements of the jaw (eg jaw opening or closure), lips (including tardive dyskinesia) or tongue.[3] Oral mandibular dystonias may be secondary to conditions such as Wilson's disease, Huntington's disease or neuroacanthocytosis, or they may be caused by drug-induced conditions such as tardive dyskinesia. The evidence base is limited to observational studies, which support possible efficacy of intervention.[11] Treatment is not PBS-funded.

Task-specific dystonias

Most commonly, focal hand dystonias affect tasks such as writing, playing music and sports. Numerous small double-blind placebo control trials indicate that writers' cramp and musician dystonia improve with BoNT. However, the degree of clinical response is not as strong as in other focal dystonic conditions such as cervical dystonia and blepharospasm.[3] Treatment is not PBS-funded.

Other indications for BoNT may include sialorrhea or hyperhydrosis associated with Parkinson's disease.[12] Conditions that require further evidence to support the use of BoNT include tics of Tourette syndrome, resting tremor of Parkinson's disease and essential tremor.[3]

Referral and funding of patients for BoNT

Patients are initially referred to a neurologist for confirmation of the diagnosis. Treatments are administered in BoNT clinics by a neurologist with expertise in movement disorders. GPs can find their nearest BoNT clinic by contacting their local neurologist. The movement disorders funded by the PBS include hemifacial spasm, cervical dystonia and blepharospasm. Although treatment with BoNT is beneficial in other conditions such as spasmodic dysphonia, task specific dystonia and oral mandibular dystonias, they are currently not supported under the PBS. Treatment of conditions not included in the PBS would typically incur additional cost to the patient, with an estimated price of $400 per vial of BoNT.

Variation in response to treatment with BoNT

Patients can have a variable response to treatment for many reasons, including:

- changing pattern of dystonia
- site of injection variation
- dosing used for treatment
- development of joint contracture
- development of BoNT antibodies
- dystonia-triggering factors such as sleep deprivation, stress and use of precipitating medications such as antipsychotics and dopamine antagonists.

Adverse effects of BoNT treatments

The most common complication is weakness due to local effects of unwanted diffusion into adjacent muscles. For the treatment of cervical dystonia, this may manifest in approximately 5% of patients as transient neck weakness and dysphagia.[3] Weakness is temporary and improves over two to four weeks. It is important that the treating clinician is aware of this complication so that the 0dose is reduced in future treatments to avoid recurrence of weakness. In rare cases, ptosis or diplopia can occur transiently for one to two weeks after injection for blepharospasm. Another rare adverse effect is transient facial muscle weakness in the treatment of hemifacial spasms, resulting in excessive drooling. Systemic adverse reactions include very rare allergic reactions, generalised weakness or a flu-like illness in the first 24 hours.[3] The formation of neutralising antibodies to BoNT can limit efficacy in the long term. However, recent studies have suggested that formation of neutralising antibodies and clinical efficacy of treatment are not always strongly correlated.[13]

Key points

- BoNT is an effective treatment for many patients with movement disorders such as cervical dystonia, blepharospasm and hemifacial spasm.

- Patients frequently experience significant disability while the condition remains unrecognised.
- GPs' recognition of the disorder is a vital first step in the management.
- Treatment by a trained neurologist with periodic (typically three-monthly) BoNT can improve quality of life, reduce pain and improve rates of return to work.

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