Botulinum toxin for spasticity: a case for change to the Pharmaceutical Benefits Scheme

Current permissible use of botulinum toxin in Australia does not match newer understanding of human impairment and functioning

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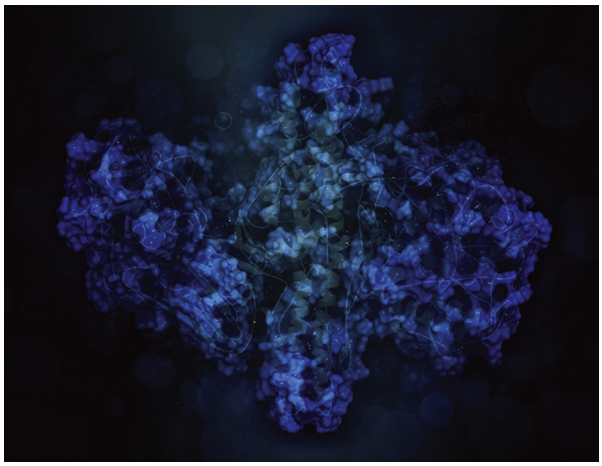
The bacterium *Clostridium botulinum* was first identified in 1895 and, in the 1950s, was first injected into a hyperactive muscle, causing flaccid paralysis by blocking the release of the neurotransmitter acetylcholine from motor nerve endings. However, the therapeutic use of botulinum toxin only became common after 1989, when it was approved for use for strabismus, and then in 2001, when it was synthesised and approved for use as a cosmetic treatment in Canada. In 2017, the idea of paralysing the muscles of the brow and face with a powerful neurotoxin for cosmetic reasons is now widely accepted, or at least conceptually understood, because of frequent reference to the popular procedure in the media.

Spasticity: a common problem for patients with neurological disorders

Perhaps less well known are the uses of botulinum toxin for rehabilitation therapies designed to assist individuals suffering the effects of a broad spectrum of neurological conditions, such as traumatic brain injury, stroke, spinal cord injury, cerebral palsy or multiple sclerosis. These disorders can be accompanied by focal spasticity caused by the malfunctioning of the upper motor neurons. Jerking, twisting and involuntary contraction of the limbs (dystonia) can accompany spasticity and may be present in Parkinson disease. Limb spasticity and dystonia can cause impaired coordination and poor motor control, weakness and fatigue. Spasticity can lead to permanent contracture, resulting in immobilised joints and ever greater disability unless it is effectively interrupted.

Patients with spasticity are assessed and managed in multidisciplinary spasticity clinics by specialist teams consisting of a rehabilitation physician or neurologist, allied health professionals and nursing staff. The team, along with the patient and their family, set goals and record the treatment outcomes in a proactive and focused process, because extensive clinical experience and new research evidence suggest that many individuals with focal spasticity and dystonia continue to live independently and function in the community with appropriate intervention. Botulinum toxin has emerged as the drug of choice for these conditions.[1,2] Use of the toxin also creates a window of opportunity within which intensive physiotherapy and other therapies can be conducted.

Although the drug has been approved for use in Australia by the Therapeutic Goods Administration (TGA), a significant number of individuals who could benefit from its use are excluded from treatment or have their treatment restricted because of the current Pharmaceutical Benefits Scheme (PBS) guidelines. Current permissible use of botulinum toxin in Australia does not match newer understandings of human impairment and functioning captured by the World Health Organization International Classification of Functioning, Disability and Health (ICF) program, which recommends that impairment be measured not just at body level (spasticity) but also by the limit to activity and the restriction of participation in society.[3,4]



Epidemiology, human and economic burden of spasticity

The epidemiological, human and economic burden of spasticity is significant.[5] The prevalence of lower limb spasticity is estimated to be 28–37% in stroke, 41–69% in multiple sclerosis, 19–92% in cerebral palsy and 13% in traumatic brain injury.[6] This means that many people who would otherwise be mobile after stroke or brain injury or during a chronic illness such as Parkinson disease are incapacitated by spasms in the muscles of their ankles or feet, as well as shoulders or hands. In Australia, for example, about 56 000 people experience stroke every year (https://strokefoundation.org.au/About-Stroke/Facts-and-figures-about-stroke) meaning that up to 22 000 people could lose mobility and independence because of painfully contorted feet and ankles. As many as 70 000 people are currently living with Parkinson disease in Australia, 10% of whom are estimated to have dystonic (curling) toes that prevent walking.[7]

Studies have shown that there are significant indirect and direct economic costs associated with the effects of spasticity.[8,9] Indirect costs relate to loss of independence, functioning and productivity, while direct costs are based on the consumption of medical resources, particularly hospital presentations. There is, for example, a fourfold increase in direct medical costs for post-stroke patients with spasticity in the first year following stroke compared with patients without spasticity.[8] The cost to quality of life may also be severe. Pain and dysfunction occur, and the conditions lend themselves to accidental falls and fracture, which are under-reported in the literature.

Assessment and treatment of spasticity

Measuring the level of spasticity is a contentious issue because no measurement scale takes account of the entire gamut of impairment. Spasticity is commonly measured using the Modified Ashworth Scale or the Tardieu Scale. Neither measures the impairment across the range of human functioning as mandated by the ICF. Newer functional measurements, such as the Berg Balance Scale, Timed Up and Go test, gait parameter analysis and goal attainment scaling are used for the lower limbs. However, no measurement methods include activity limitation or participation restriction as directed by the ICF. The Caregiver Burden Scale and quality of life measurements are also not considered, although the cost is manifest and real.

Treatment of spasticity is multimodal and includes medications, physiotherapy, orthotic care, intrathecal baclofen, chemical denervation, and the use of botulinum toxin. Pharmaceuticals used are baclofen, dantrolene, diazepam, tizanidine and gabapentin. Some patients may also require surgery if spasticity has given rise to persistent contracture.[9]

Unfortunately, medications have significant side effects in many patients,[10] and botulinum toxin has emerged as the drug of choice for focal spasticity and dystonia because treatment can be targeted and a single treatment can last up to 4 months.[11]

PBS and guidelines

In Australia, drug approval requires applying to the TGA with data demonstrating the safety, quality and effectiveness of the product and its need in Australia. Once approved, the drug appears on the Australian Register of Therapeutic Goods. The TGA decision to register a drug is based solely on its safety and efficacy.

The manufacturer then applies to the Pharmaceutical Benefits Advisory Committee for the drug to be included in the PBS schedule, which would allow it to be subsidised by the Australian government, making it affordable to all Australians. The Pharmaceutical Benefits Advisory Committee takes into account the medical conditions for the drug, comparison of effectiveness to existing therapies, cost-effectiveness compared with existing therapy, and patient and doctor feedback.

The current PBS indications for botulinum toxin are:

- dynamic equinus deformity due to spasticity in ambulant patients with cerebral palsy (aged 2–17 years) and in patients ≥ 18 years if they commenced treatment as a child;
- upper limb spasticity in children with cerebral palsy (aged 2–17 years inclusive) and in patients ≥ 18 years if they commenced treatment as a child; and
- moderate to severe (≥ 3 on the Modified Ashworth Scale) upper limb spasticity after stroke in adults (restricted to four doses per limb).

It is clear that current guidelines restrict the use of botulinum toxin, supporting intervention only for cerebral palsy and upper limb post-stroke spasticity. For cerebral palsy, only adults who were treated as children can receive botulinum toxin, in spite of the fact that current research and clinical experience suggest that adult patients with cerebral palsy respond well to the toxin.[12] For instances of stroke, while upper limb spasticity post-stroke can be treated (minimally), post-stroke lower limb spasticity and foot dystonia are excluded, although the reduction of both is critical to walking.[13]

Unfortunately, the PBS guidelines reflect outdated information about the treatment of spasticity in either the upper or lower limbs following stroke (and other neurological disorders). Several methodological flaws such as inappropriate patient selection, injection protocols and study designs were reported with botulinum toxin trials.[14] More recent studies[15] with stronger methodologies have been very positive and have persuaded the United States Food and Drug Administration to approve the use of botulinum toxin in lower limbs during recovery from stroke. Studies have shown the cost-effectiveness of botulinum toxin treatment.[8,9] Despite this recent evidence, the PBS has not acted to update Australia's approach to botulinum toxin application.

Many issues associated with limb spasticity relate to basic human dignity, and randomised control trials are frequently not feasible because of small numbers or for purely ethical reasons. The best evidence of a treatment's efficacy is often revealed through powerful patient experiences and narratives. The PBS needs to be cognisant of this and give greater weight to rehabilitation concepts that affect quality of life. These include passive functions, examples of which include being able to move with sufficient limb comfort and control to wear shoes and socks, to toilet privately or to wash one's hands.

Frustration with inconsistencies between the TGA approval and the PBS recommendations in Australia resulted in the Rehabilitation Medicine Society of Australia and New Zealand publishing a position statement on the therapeutic use of botulinum toxin in rehabilitation medicine for spasticity and dystonia in 2013 and again in 2017. The Society's expert committee, in concurrence with an international consensus, suggested a multidisciplinary approach in the management of focal spasticity and dystonia, and argued that the decision to treat should be based on the potential to reduce

impairment and limitations in activity and participation.[16]

The way forward

Management of spasticity and dystonia should not be restricted to narrow focus and limited insight and is best guided using the paradigm promoted by the ICF. The PBS should allow extension of treatment with botulinum toxin, with a multidisciplinary team setting goals and recording outcomes in consultation with the patient. New trials should be undertaken with appropriate methodological rigour, adequate sample size and functional outcomes.

Spasticity can be moderated safely and effectively in both upper and lower limbs with botulinum toxin and the input of a skilled multidisciplinary team. Individuals with spasticity are already disadvantaged by their condition; they should not be further disadvantaged by ignoring effective treatment options.

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