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## BOTULINUM TOXIN

### **A Position Statement of the NSW Therapeutic Assessment Group Inc.**

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This review was prepared by the author in consultation with members of the NSW Therapeutic Assessment Group Inc.

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## **EXECUTIVE SUMMARY**

Botulinum Toxin type A causes muscle paralysis by binding to pre-synaptic nerve terminals. It is used therapeutically for a range of dystonias that have historically responded fairly poorly to surgery or pharmacological alternatives. The toxin has general marketing approval in Australia for blepharospasm and hemifacial spasm in patients twelve years and over.

The NSW Therapeutic Assessment Group believes that there is sufficient evidence to support the use of botulinum toxin in the following indications:

1      **Blepharospasm**

As first line therapy, with injections repeated every 3-4 months while the patient continues to tolerate and respond to therapy.

2      **Hemifacial spasm**

As first line therapy, with injections repeated every 4-5 months while the patient continues to tolerate and respond to therapy. Microvascular decompression may be a more suitable therapeutic option for selected patients

3      **Laryngeal dystonia**

As first line therapy although patients may be offered surgery as an alternative option.

4      **Spasmodic torticollis**

As second line therapy, particularly in those with jerky mobile torticollis, retrocollis and anterocollis, when alternative pharmacological agents have been unsuccessful or poorly tolerated. Patients receiving botulinum toxin should be assessed after 2-3 doses for objective response and therapy continued only in those achieving significant benefit and tolerable side effects.

All other uses of botulinum toxin should be within controlled clinical trials or following individual patient approval as there is either insufficient evidence of efficacy or tolerability in reports currently available.

Approximately 900-1200 patients may be eligible for continuing treatment under these guidelines at a cost in NSW of two-three million dollars per annum. Because of the high doses required and the relatively larger number of patients with spasmodic torticollis, the level of usage in this group will be significant in determining the final costs.

# 1 INTRODUCTION

Botulinum toxin type A, one of the most lethal biological toxins known, has been found to be therapeutically valuable in several neurological and ophthalmological disorders.

The toxin causes muscle paralysis by binding to the pre-synaptic cholinergic nerve terminals. It enters the nerve cell and inhibits the release of acetylcholine<sup>1</sup>. When used therapeutically, botulinum toxin produces a localised muscle paralysis by chemical denervation. When the muscle is denervated, it atrophies and develops extrajunctional acetylcholine receptors<sup>1,2</sup>.

Cultures of *Clostridium botulinum* are purified by a series of acid precipitations to a crystalline complex consisting of the haemagglutinin protein and the active toxin protein<sup>1</sup>. Most reported studies refer to botulinum toxin produced in the United Kingdom or the United States. There is a difference in the potency as expressed in units per nanogram of these preparations<sup>3</sup>. One unit of toxin corresponds to the LD50 in mice of the preparation but there are also differences in the bioassay result hence one US mouse unit is equivalent to 4.4 UK mouse units<sup>4,5</sup>. In this report we will refer to US mouse units unless otherwise indicated.

Botulinum toxin is supplied by Allergan Australia Pty Ltd in Australia. It has general marketing approval for the treatment of blepharospasm associated with dystonia and seventh nerve disorders (specifically hemifacial spasm) in patients twelve years and over.

## 2 CLINICAL TRIALS AND APPLICATIONS

### 2.1 Dystonia

Dystonia is a syndrome of sustained, involuntary, muscle contraction, frequently causing twisting and repetitive movements or abnormal postures<sup>2</sup>. Focal dystonias such as blepharospasm, torticollis, oromandibular dystonia, laryngeal dystonia and task-specific dystonias have been treated with a variety of therapeutic approaches. These include education, psychotherapy, biofeedback, drug therapy, myectomy and neurectomy<sup>2</sup>.

Surgery is initially effective in some types of dystonia but it is associated with a high recurrence rate<sup>2,6</sup>. Drug therapy which includes clonazepam, diazepam, benzhexol, baclofen, orphenadrine, levodopa and lithium carbonate<sup>2,7,8</sup> achieves partial symptomatic relief in 20-50% of patients. Benzhexol and levodopa appear to be the most successful of these pharmacological options<sup>2</sup>.

#### Epidemiology of dystonia

An epidemiological study of dystonia in the population living in Rochester, Minnesota indicated that the prevalence of focal dystonia was 30 per 100,000<sup>9</sup>. The incidence in Australia is likely to be similar. The most common idiopathic focal dystonia referred to a large medical dystonia research centre in the USA was torticollis (44%), followed by spastic dystonia (25%) and blepharospasm

(14%)<sup>10</sup>. This may underestimate the number of patients with blepharospasm due to referral bias. In the United Kingdom, there are approximately 10,000 people with torticollis and 5,000 each with blepharospasm and hemifacial spasm<sup>11</sup>. Therefore in Australia, it is estimated that there would be approximately 15 patients per 100,000 population with torticollis and half this number for each of hemifacial spasm and blepharospasm.

### **2.1.1 Blepharospasm**

Blepharospasm is a focal dystonia characterised by intermittent or sustained eye closure due to repetitive, involuntary contractions of the orbicularis oculi muscle.<sup>12</sup>

Twelve patients with blepharospasm were randomised to receive botulinum toxin or saline placebo in a double-blinded cross-over study<sup>13</sup>. All twelve patients improved ( $p < 0.005$ ) after a total of 14 serial injections of botulinum toxin and showed a 71.6% improvement over baseline on self-assessment scores ( $p < 0.01$ ) and a 38.9% improvement on videotape score ( $p < 0.04$ ). The mean duration of improvement was 12.5 weeks.

Open studies have found similar results with relief of symptoms being reported in 69-100% of patients for mean periods of 3-4 months<sup>14-17</sup>. Reversible complications have been reported in approximately 20-30% of patients<sup>17,18</sup>. Long-term use appears to offer continued benefits for most patients<sup>18</sup>.

### **2.1.2 Spasmodic Torticollis (Cervical Dystonia)**

Spasmodic torticollis is a dystonia affecting the neck muscles which produces tonic or clonic movements which cause the head to deviate in any direction. Spontaneous remission is said to occur in 10-38% on patients although this is rarely sustained in the long-term<sup>8,15</sup>.

A randomised, double-blind, controlled clinical trial in 55 patients who had failed at least two previous drug therapies found that maximum response to botulinum toxin occurred 6 weeks after administration<sup>19</sup>. When given a dose of 145 units per patient and assessed at six weeks, the results of botulinum therapy were: 11% of subjects reported worsening of symptoms, 29% reported no improvement, 21% reported minimal improvement, 29% reported moderate improvement and 11% marked improvement. The placebo arm of this study was discontinued after 12 weeks and an open label study using higher doses of botulinum toxin (240 units / person) commenced. A response rate of 74% was reported for this phase.

A second study<sup>20</sup> in twenty patients found that 60% of patients recorded subjective improvement after two doses of botulinum toxin (500 units British toxin per dose), two weeks apart compared with 20% of patients on placebo ( $p < 0.05$ ). The video-taped assessment in this study did not show a clear improvement in those receiving active treatment but an inadequate washout period in the cross-over design of the study may be partly responsible for this. Effectiveness was apparent 5-10 days after the first injection but occasionally was not seen until a week after the second injection. The duration of improvement was 8-10 weeks.

Twenty patient with isolated torticollis were injected with three doses of botulinum toxin and placebo in two to four neck muscles<sup>21</sup>. The order of injection was randomised and re-injection only performed after the benefits of the previous injection had completely disappeared. Subjective assessment found that 80% of those receiving botulinum toxin reported a favourable response although only 55% reported substantial improvement. This compared with 25% of patients reporting a favourable response to placebo. Objective response, as determined by videotaped assessment, was found to be favourable in 60% of those receiving botulinum toxin but this was only substantial in 15% of patients. Additionally, 45% of patients showed objective deterioration after at least one injection of botulinum toxin. Of the doses used in this study, optimal effects were observed with 100-140 units per patient (20-90 units per muscle). Botulinum use in torticollis has been associated with an increased incidence of dysphagia<sup>22</sup>.

An Australian, double-blind, placebo-controlled study was conducted in 23 patients who were unresponsive to optimal alternative pharmacological treatment<sup>23</sup>. Patients were assessed by their clinician, by two blinded clinicians viewing video footage, subjectively by patients and for improvement in pain. The results showed that: when assessed by the clinician, 87% of patients improved on botulinum toxin compared with 17% on placebo ( $p < 0.001$ ); when assessed from video footage, 61% improved on botulinum toxin compared with 4% on placebo ( $p < 0.01$ ); when assessed subjectively, 78% improved on botulinum toxin compared with 17% on placebo ( $p < 0.001$ ); and when assessed for effect on pain, 52% improved on botulinum toxin compared with 4% on placebo ( $p < 0.002$ ).

### **2.1.3 Oromandibular Dystonia**

Dystonic movements of the jaw, tongue and lower facial muscles can give rise to trismus, bruxism, involuntary tongue movement and opening, closure or deviation of the jaw.

An open label trial of botulinum toxin (dosage individualised but not specified) in 20 patients found that seven patients had 0-10% improvement, one patient had a 10-20% improvement, three patients had 50% improvement and nine patients had  $\geq 75\%$  improvement in symptoms by patient self-assessment<sup>24</sup>. Treatment of jaw closing dystonia has been reported to be more successful than other types of oromandibular dystonia with an average improvement in function of 70%<sup>15</sup>.

### **2.1.4 Laryngeal Dystonia (Spastic or Spasmodic Dysphonia)**

Laryngeal dystonia is an action-induced dystonia, characterised by a strained, strangled or breathy voice, frequently interrupted by voiceless pauses and whispering. Conventional treatment with recurrent laryngeal nerve section has a long term success rate of 36%.

A double blind, placebo controlled study carried out in 13 patients with adductor spasmodic dysphonia used 5 units botulinum toxin or saline injected into each thyroarytenoid muscle<sup>25</sup>. Patients receiving botulinum toxin had no difference in fundamental frequency measurement or

phonation time measurement but reduced vocal fundamental frequency range and better perturbation scores when sound spectrograms were analysed. Speech ratings from videotaped sessions before and after treatment showed significantly more improvement in those who received botulinum toxin and self-assessment also showed improved results.

A larger study in 320 patients, 260 with primary and 60 with secondary laryngeal dystonia, was conducted in an open-label design, using individualised doses of botulinum toxin (1.25 to 3.75 units)<sup>26</sup>. All patients were reported to experience benefit, with therapy becoming effective in the first 24 hours, followed by a period of hypophonia that was maximal on the third post-injection day and which continued for 4-14 days. Speaking improved by a mean 90% and the beneficial effect lasted for 3 to 4 months. Patients with abductor laryngeal dystonia do not respond as well to botulinum therapy with a mean improvement in speaking of 57% and a return to mean maximal function performance to 80% of normal.

### **2.1.5 Other Dystonias**

Hand and limb dystonias which include writer's cramp and musician's cramp, can be among the most occupationally disabling of all dystonias.

Use of botulinum toxin in 53 patients with hand dystonia for up to six years demonstrated an 81% response to treatment<sup>27</sup>. However, only 25% of patients in this study elected to continue with injections in the long-term (mean treatment period of 3 years). The remaining patients were lost to follow-up, elected to discontinue therapy (after a mean of seven sessions) or were unable to continue for logistical reasons.

Seventeen patients with limb dystonias were treated with botulinum toxin and placebo in a double-blinded, randomised cross-over study design<sup>28</sup>. Subjective response was observed in 82% of those receiving botulinum compared with 7% on placebo. The improvement in botulinum-treated patients was substantial in 59% and its duration ranged from 1-4 months. Objective benefit was reported in 59% of patients on botulinum toxin compared with 38% on placebo and there was no statistical difference between these results. Side effects were reported in 53% of patients receiving botulinum toxin and 13% receiving placebo.

A double-blind cross over comparison of botulinum toxin and placebo in twenty patients with severe symptoms of writers cramp found that speed and accuracy of pen control improved significantly ( $p < 0.05$ ) after treatment with botulinum toxin<sup>29</sup>. Sub-group analysis suggested that patients with significant wrist-joint deviation were most likely to respond ( $p = 0.001$ ). Subjectively, eight of the 12 patients who had pain associated with writer's cramp reported relief after botulinum injection.

## **2.2 Hemifacial Spasm**

Hemifacial spasm is a movement disorder of the face characterised by involuntary, recurrent, episodic, twitching, tonic spasm and synkinesis of the muscles innervated by the facial nerve. Drug therapy, including carbamazepine, baclofen and clonazepam has been found useful in a small number of patients. In selected patients, success rates of over 90% have been reported with decompression of the facial nerve in the posterior fossa to relieve symptoms<sup>14</sup>.

Complete or almost complete relief of symptoms has been reported in 90-100% of patients receiving botulinum toxin for hemifacial spasm for periods of three to four months<sup>14</sup>.

Of twenty patients with hemifacial spasm who received 44 treatments, 93.1% demonstrated total relief of periocular and perioral spasm for a mean period of 17.4 weeks<sup>30</sup>. The duration of response appeared to decline with continued therapy, being significantly shorter after the third treatment session than for the first two sessions.

In another study<sup>31</sup>, fifteen patients treated with botulinum toxin for up to 30 months were found to have a response rate of 93% for a mean interval of 17.25 weeks. Eighteen percent of patients required higher than the standard dose for therapeutic effect.

### **2.3 Other applications**

Botulinum toxin may have limited application to the management of strabismus, particularly for patients with recent surgical overcorrections and management of sixth cranial nerve palsy<sup>32,33</sup>. It has also been used with some success in spasticity associated with chronic stable multiple sclerosis<sup>34</sup>, tremor<sup>35</sup> and achalasia<sup>36</sup>. It probably has very limited usefulness in nystagmus with regular periodicity because of side effects<sup>37</sup> but may have a role in chaotic eye movement disorders such as oscillopsia and opsonclonus<sup>38</sup>.

### **3.0 ADVERSE EFFECTS**

Botulinum toxin causes several adverse effects which are related to its mode of action and site of administration. All adverse effects resolve with time.

In patients treated for blepharospasm, the most common complications are ptosis (11-23%), blurred vision, dry eyes (10-17%) and tearing (5%)<sup>14,39</sup>. Ectropion, keratitis, diplopia and entropion have been reported less frequently<sup>37</sup>.

In eighteen patients treated for torticollis, symptomatic dysphagia was present in 11% of patients prior to botulinum toxin and in 44% of patients following treatment<sup>21,22</sup>. Symptoms began after 1-10 days (mean 5.3 days) and lasted from 4-42 days (mean 15.8 days). In the same study, 22% of patients had radiological evidence of dysphagia pre-treatment compared with 55% after botulinum treatment. In other studies, the incidence of side effects in patients treated for torticollis has been dysphagia 10-35% (versus 0% with placebo), dry, sore throat 30% (versus 0.5% for placebo), local weakness 25% (versus 0% with placebo) and regional pain 5-30% (versus 15-25% with placebo)<sup>20,21</sup>.

In patients treated for dysphonia, side effects include excessive breathiness of the voice (15-45%), mild choking on fluids (22%) and mild bleeding from the throat ( 7%)<sup>25,26</sup>.

Transient local weakness has been reported with 53% of injections for limb dystonia<sup>28</sup>.

Patients treated for hemifacial spasm with botulinum toxin may experience facial weakness, weakness of lip elevation and other side effects experienced by patients with blepharospasm<sup>7,15</sup>.

### **Antibody Formation**

Antibodies to botulinum have been reported in 3-4.3% of patients with some correlation between total dose and antibody formation<sup>40,41</sup>. In order to minimise the risk of developing botulinum toxin resistance, it is recommended that the toxin be injected as infrequently as possible (certainly no more frequently than every four weeks) and that the lowest dose of toxin be used. Antibody development is unlikely to occur in conditions where low doses of toxin are effective such as in spasmodic dysphonia and hemifacial spasm.

## **4 RECOMMENDATIONS**

NSW Therapeutic Assessment Group conclude that sufficient evidence is available to support use of botulinum toxin in the following indications:

### **4.1 Blepharospasm**

Botulinum toxin is considered safe and effective primary therapy for patients with blepharospasm.

Dosage: 1.25 to 2.5 units injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal or preseptal part of the orbicularis oculi of the lower lid is initially recommended. Dosage may be increased on subsequent treatments up to a maximum total dose of 25-60 units. Repeat injection will be required every 3-4 months in patients but should only be offered to patients who continue to respond to or tolerate treatment. It should be administered by a medical practitioner experienced in its use.

### **4.2 Hemifacial spasm**

Botulinum toxin is considered safe and effective primary treatment of hemifacial spasm. Consideration should be given to microvascular decompression in selected patients, including patients less than 50 years old and in whom there is severe facial weakness; the latter is likely to be exacerbated by botulinum toxin.

Dosage: Initially 5 units of botulinum toxin is injected into the periocular muscles on the involved side of the face and to the lower facial muscles if applicable. Injection may be repeated every four to

five months but should only be offered to patients who continue to respond to or tolerate treatment. Dosages up to 50 units for the whole side of the face. It should be administered by a medical practitioner experienced in its use.

### **4.3 Laryngeal Dystonia**

In view of the relatively poor long-term success rate of surgery, it is reasonable to offer botulinum as first line therapy. Patients with adductor laryngeal dystonia are expected to achieve better efficacy from botulinum toxin than those with abductor laryngeal dystonia. The prolonged period of hypophonia following treatment (approximately two weeks) may make botulinum toxin unacceptable to some patients, although the hypophonia always recovers.

Dosage: A dose of 1-5 units of botulinum toxin injected into each thyroarytenoid muscle has been recommended by the manufacturer. There is some debate, however, as to whether the most appropriate administration is by unilateral thyroarytenoid injections which may cause fewer side effects. In the case of unilateral injection the dose is 10-15 units<sup>42</sup>. It should be administered by a medical practitioner experienced in its use.

### **4.4 Spasmodic Torticollis**

Botulinum toxin should be considered for those patients who do not respond to alternative pharmacological agents such as benzhexol and levodopa. Unfortunately only a small number of patients can be expected to respond to or tolerate these drugs. However, because of the relatively high incidence of side effects and a reported efficacy in only 50-60% in patients with torticollis, botulinum toxin is not recommended as first line therapy at the present time. This recommendation will require review should better efficacy and safety data become available. It is likely that treatment will be cost-effective only in those who experience moderate to substantial improvement in their dystonia and little or no dysphagia. Patients with rotational torticollis or laterocollis where the direction is consistent and abnormal posture is the main clinical feature will be expected to achieve more substantial benefits with botulinum toxin.

Dosage: Intramuscular injection of 50 to 75 units to each of the two-four muscles most affected by spasm is recommended up to a total dose of 150-300 units per patient. Injections may be repeated approximately every three months but should only be offered to patients who continue to respond to or tolerate treatment.

### **4.5 Recommended for Use Within Controlled Clinical Trials or After Individual Patient Approval Only**

- 1 Strabismus
- 2 Hand and limb dystonias
- 3 Chaotic eye movement disorders which decrease vision
- 4 Oromandibular dystonia (particularly jaw closing dystonia)

- 5 Spasticity
- 6 Tremor

#### **4.6 Not Currently Recommended for Use**

- 1 Nystagmus with regular periodicity
- 2 In pregnancy
- 3 Extreme caution should be exercised if using botulinum toxin in patients with neuromuscular transmission disorders.

### **5 ECONOMIC CONSIDERATIONS**

Given the epidemiology of dystonias and hemifacial spasm, up to 1500 patients may be eligible for treatment in New South Wales under the NSW TAG guidelines. Of these, 40-90% of patients would be expected to respond to therapy and some patients will elect to discontinue therapy because of adverse effects. Therefore, approximately 1200 patients may receive relatively chronic treatment in NSW based on the criteria in these guidelines.

For torticollis, the dose per patient is up to ten fold greater and the duration of effect is shorter than for other indications. The data currently available also suggests that botulinum toxin is less effective in this condition, therefore raising questions of its cost-effectiveness.

In Australia, the cost of botulinum toxin is \$4.50 per unit. Assuming the use of a multidose vial for several patients, the average annual cost to treat a patient with blepharospasm is approximately \$900 per year compared with torticollis which would be \$5,500 per year. The cost in NSW under these circumstances would be expected to be approximately two to three million dollars per annum.

The recent Section 100 arrangements of the pharmaceutical benefits scheme make botulinum toxin available free of charge to patients seen by a specialist medical practitioner under private health care arrangements. Each dose of botulinum would be prepared from a new vial under these arrangements, substantially increasing the costs of drug usage. Under these arrangements, the drug costs alone of botulinum toxin used in NSW could escalate to four million dollars per annum.

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