Movement, visceral and autonomic disorders: use of botulinum toxin

A Peter Moore

This article reviews the development of botulinum toxin treatment, how it works, the range of conditions it can treat and the benefits and side effects. It sets out how it is used in practice in specialist units.

Over the last 15 years our view of botulinum toxin (BTX) has changed. Since its first use in 1977 there has been a steady stream of new indications and involvement of new specialties (Naumann et al, 2003). Its uses now range from the cosmetic to treatment of highly debilitating diseases. There is a pattern of anecdotal reports of benefit in a new indication followed by multiple small, uncontrolled or open studies, and eventually controlled and blinded trials appear, some of which support the use of BTX. For some indications uncritical initial enthusiasm has created an atmosphere inhibiting adequate controlled trials, and has left purchasing authorities in a quandary.

This review describes the development of BTX treatment, how it works, the range of conditions it can treat, and how it is used in practice in specialist units. Strictly speaking, much expert practice with BTX remains 'off-licence' and unproven. Where relevant the author tells patients and carers that BTX is off-licence or is experimental, and they must accept this. Signed consent must always be obtained before starting any course of BTX treatment.

HISTORY

The concept of botulinum toxin was discovered by Justinus Kerner (1786–1862), a German physician in the 19th century, when he deduced that a type of systemic food poisoning known since Roman times was caused by a neurotoxin that acts by interrupting signal transmission within the peripheral motor, sympathetic and parasympathetic nervous systems, leaving sensory signal transmission intact. He even realized that the toxin might one day make a useful treatment, for instance for problems resulting from an overexcited autonomic system such as excessive sweating. He suggested that the toxin would help in St Vitus' dance, which was at that time thought to be caused by sympathetic overactivity. In 1870, the German physician Müller first used the term 'botulism' (from the Latin word botulus = sausage) to describe the effects of sausage poisoning, the most common source of outbreaks of this kind of systemic food poisoning. Emille Pierre van Ermengem, a professor of microbiology in Ghent, isolated the bacterium *Clostridium botulinum* in 1895.

Progress was then slow until Dr Carl Lammanna crystallized BTX type A (BTXA) in 1946, and later clarified its structure (Naumann et al, 2003). Burgen et al (1949) discovered that BTXA blocked the release of acetylcholine at neuromuscular junctions. Schiavo et al (1993) showed that the BTX serotypes are all metalloproteases specific for three proteins that form the core of the neuroexocytosis machinery – the 'SNARE' (SNAp [soluble N-ethyl-maleimide sensitive factor attachment protein] receptor) proteins (Schiavo et al, 1994). Recently, the shape and functional domains of these complex molecules have been clarified, and their mechanisms of action are increasingly well understood.

MECHANISM OF ACTION

The toxins work by causing chemical denervation of structures served by cholinergic neurones (Rosetto and Montecucco, 2003). They form a group of seven known antigenically distinct zinc-dependent metalloprotease enzymes labelled BTXA–G, secreted naturally by various strains of *C. botulinum*, and can be harvested from bacterial cultures. They are the most potent neurotoxins known. Note that the toxins are chemicals, and not live organisms. In their active forms the toxins are two-chain molecules, or dimers, with the chains linked by a disulphide bridge.

The H- (heavy) chain is a highly specific targeting device which attaches only to special acceptor molecules on the terminals of choliner-

Mr A Peter Moore is Senior Lecturer in Neurology, The Walton Centre for Neurology and Neurosurgery, Liverpool L9 7LJ

gic nerves. The cell actively endocytoses the toxin into the nerve terminal. Once inside the nerve terminal the H-chain engineers passage of the toxin complex through the wall of the endocytosed vesicle into the cytoplasm in an energy-dependent step, and the L- (light) chain dissociates from the H-chain. The L-chain is the toxic element and damages part of the protein molecular machinery responsible for docking vesicles to the nerve terminal membrane (SNARE proteins). In theory, because BTX is an enzyme, a single molecule could destroy all of the target protein in that cell.

Each BTX subtype attacks a different part of the SNARE machinery, but the clinical effect is similar: the vesicle cannot dock properly with the membrane, and release of its contents is inhibited or blocked. Cells other than cholinergic nerve terminals are protected by their lack of H-chain receptors, but SNARE proteins are found in most cells, and if L-chains are inserted experimentally into other cells they have an equivalent effect. In cholinergic α-motorneurone nerve terminals the result is a failure to release acetylcholine, blockade of the neuromuscular junction, and muscle weakness and atrophy. BTX can block all cholinergic nerve cells in this way, including autonomic cells, so can suppress sweating, salivation, pupillary reactions and gut peristalsis. The evolutionary advantage of this to *C. botulinum* is obscure.

The effects are temporary. The toxic L-chains are presumably degraded and become inactive, and the damaged proteins can be replaced. In muscles the weakness and atrophy resolve over several months during which multiple new rudimentary nerve–muscle synapses form and then regress as the original neuromuscular junctions recover.

CLINICAL USE

Table 1 summarizes the range of conditions treated and the evidence that botulinum toxin works in various indications. Alan Scott was the first to treat a patient with BTXA when he injected the toxin in a patient with strabismus in 1977 (Scott, 1979). By 1982, he had also treated patients for nystagmus, hemifacial spasm, lid retraction, torticollis and spasticity. After its initial success in treating strabismus, BTXA has revolutionized treatment for many neurological and ophthalmic diseases, and is used in cosmetic, general, orthopaedic and thoracic surgery, dermatology, otorhinolaryngology, pain clinics, paediatrics, rehabilitation medicine and urology. *Table 1* shows the various indications for its use and the strength of the evidence supporting its use. These disorders are characterized by focal

TABLE 1.
Range of conditions treated and strength of evidence*

Focal dystonias		Blepharospasm	+++
		Cervical dystonia	+++
		Spasmodic dysphonia	+++
		Meige syndrome	++
		Writer´s cramp	++
		Foot dystonia	++
		Occupational cramps	+
		Oromandibular dystonia	+ +
		Axial dystonia	+
Tremor		Dystonic head tremor	++
		Essential head tremor	++
		Essential hand tremor	+
		Palatal tremor	+++
Hemifacial spasm			+++
Focal spasticity in adults		Lower limb	++
		Upper limb	++
Focal spasticity in children		Lower limb	+++
		Upper limb	++
Ophthalmological indications		Strabismus	++
		Sixth nerve palsy	+
		Nystagmus and oscillopsia	+
		Protective ptosis	+
Autonomic indications	Secretory disorders	Focal hyperhidrosis	+++
		Gustatory sweating	+++
		Hyperlacrimation	++
		Sialorrhea	++
	Urological indications	Detrusor sphincter dyssynergia	+
		Hyperreflexic bladder	+
		Urethrism	+
		Vaginismus	+
	Gastrointestinal uses	Anal fissure	+++
		Achalasia	++
		Upper oesophageal sphincter	+
		Outlet constipation	+
		Anismus	+
		Sphincter of Oddi	+
Pain		Tension-type headache	+
		Migraine	+
		Backaches	+
Wrinkles			++
Other unusual indications		Tics	+
		Stiff person	+
		Rigidity	+
		Bruxism	+
		Myokymia	+

*This list is not exhaustive. It is a guide, and represents a best fit rather than a precise classification. +++ = accepted indication, conclusive evidence, effective treatment; ++ = often used indication, reasonable trial evidence, moderately effective; + = sometimes used indication, inconclusive trial evidence, efficacy possible, but not clear. From Naumann et al (2003)

muscle or localized autonomic overactivity, and the rationale for using BTX relates clearly to the known mechanism of action. BTX is also being tested in various pain syndromes, such as migraine, tension-type headache and back pain, where the rationale is less clear, as the link between the pathophysiology of the pain and muscle or autonomic activity is at best muddy.

In 2001, another serotype of the neurotoxin – BTXB – was licensed for cervical dystonia, and it is undergoing testing for many of the diseases currently treated with BTXA. Other serotypes such as types F and E are under evaluation.

PRINCIPLES OF CLINICAL USE

In clinical use, BTX is usually injected intramuscularly into carefully selected muscles or glands (Moore and Naumann, 2003). Its effect is concentrated in the injected structures so that highly focal weakness or reduced secretion can be generated. Susceptible muscles range from the largest to the smallest. For instance in spasticity, knee extension spasms may stop after injection into the quadriceps. Palatal myoclonus or spasmodic dysphonia can be abolished by BTX injections in the soft palate and vocal cord muscles respectively.

BTX takes effect gradually after several days to weeks, and causes clinically detectable weakness and atrophy or reduced secretion for 2–4 months in most situations, sometimes rather longer. It wears off gradually. The degree and to some extent duration of the effects are dose-dependent, and the concentration of BTX seems less critical (Shaari and Sanders, 1993). Weakened muscles always recover if left long enough. Repeat injections follow the same course and biological tolerance is unusual.

BTX is rarely a cure. It is a symptomatic treatment and is likely to need repeating at regular intervals. In conditions such as focal dystonias it may be sufficient treatment, in others it is one component of a wider programme of treatment. BTX can reduce the need for other treatments. Some patients with widespread relatively mild spasticity have additional severe focal spasticity. Injecting the more severely affected muscles might allow reduced systemic medication. Sometimes blocking the most severe spasticity reduces general levels of noxious stimulation and indirectly allows widespread reduction of muscle tone.

Occasionally, the clinical benefit of BTX greatly outlasts the induced weakness. When an ocular muscle is weak, causing squint, BTX injection of the antagonist muscle can straighten the eye and establish binocular vision. Binocular fusion mechanisms may then be sufficiently powerful to maintain binocular vision even when the toxin-induced weakness has cleared. Early treatment of spasticity could in theory break a cycle of spasm, pain, fibrosis and contracture and influence remodelling of central circuits. It assists physiotherapy by making it easier to manipulate limbs and retrain antagonist muscles, and allows more comfortable and better tolerated splinting. Indeed, the best effects of BTX treatment may only be obtained when combined with physiotherapy and splinting — and vice versa. Dystonias may die down for a year or more and this may be the result of a coincident remission.

WHICH PATIENTS BENEFIT?

It is better to understand the principles of selection than learn a list of indications. Any patient with persistent and relatively focal muscle or (appropriate) glandular overactivity may benefit, almost independently of the cause. The associated reduction in muscle-spasm-induced pain can be as useful as improvement in posture or involuntary movements. Muscle hypertrophy may interfere with function or look unsightly, as in masseteric hypertrophy, and BTX-induced atrophy may be greatly appreciated. Correction of cosmetic defects can restore a recluse to normal social life; examples include facial asymmetry, involuntary grimacing or limb distortions.

Many patients with an incurable primary disorder develop symptoms that BTX can help, such as sialorrhoea in parkinsonism or motor neurone disease. In experienced hands a certain amount of imagination can pay dividends by helping in unusual situations. For instance, some patients with spasticity have such severe arm flexion spasm that they can choke themselves or induce blackouts through carotid sinus pressure — BTX can weaken the spasms enough to abolish both the choking and blackouts. Such indications are never likely to be subject to randomized controlled trials because these are such rare cases.

The decision to use BTX depends on the ease of muscle selection for injection and whether the toxin can be delivered precisely. This can be technically demanding, as in writer's cramp, yet can be straightforward provided the clinician has a good understanding of local anatomy and muscle dynamics. In focal dystonias, clinicians pick muscles that are tender, hypertrophied, visibly or palpably contracting, or are clearly responsible for the involuntary posture or spasm. Sometimes these criteria conflict or the posturing is complex, as can occur in torticollis. Video recording or multichannel electromyographic recordings may help.

AVAILABLE PREPARATIONS AND DOSES: A HAZARD WARNING

BTX doses are measured in mouse units (mu), based on a mouse LD50 test. This defines one unit as the dose that would have a 50% chance of killing a mouse (when injected intraperitoneally). Unfortunately, despite this attempt to standardize doses the various commercially available BTX preparations require completely different clinical doses (*Table 2*), probably as a result of different species sensitivities. It is essential to select the correct dose schedule or convert accordingly. Conversion factors are not tightly defined, with conflicting results from clinical studies, and it is best to follow the individual manufacturer's recommendations. Note also that early reports of BTXA trials commonly do not specify the preparation used, and one even used the term 'Botox' generically when the study used Dysport (Dengler et al, 1992). Some studies have combined results from patients using different preparations. BTXB (NeuroBloc/MyoBloc, Elan) doses are different again.

BTX doses are generally highest in spasticity, and are limited by the risk of local side effects or systemic toxicity (botulism). We do not know the upper limits with certainty. Most clinicians allow up to 1500 mu Dysport-equivalent in a single adult injection session. A few will go up to 2000 mu, with an increasing risk of causing systemic botulism, and also of provoking antitoxin antibodies (see below). There is one report of occasional patients developing systemic symptoms at moderate doses after many previous injections of similar doses (Bhatia et al, 1999). This is extremely unusual. If such patients receive further injections at the same dose they may revert to their previous good response.

MATCHING THE DOSE TO THE PATIENT

Experience has generated 'standard' doses which work for most patients and provide a good starting point. As a guide the dose should be increased for hypertrophied or highly active muscles and reduced in:

1. Small or lightweight patients
2. Cases where the target muscles are already weak
3. Cases where there is a special risk of side effects (this may be a low risk of a serious effect such as dysphagia after neck injections, or a high risk of a minor effect).

Pre-existing local tissue disruption (recent trauma, infections) or systemic weakness, such as in myopathy, myasthenia gravis, motor neurone disease or neuropathy, should provoke extreme caution, but are not absolute contraindications. Treatment of dystonia needs smaller doses than spasticity in the same muscles. Experienced clinicians modify the initial dose accordingly, and assess the effects after each injection session in order to optimize the dose next time.

START HIGH OR START LOW?

In some situations the author uses a cautious strategy with modest doses on the first injection session, titrating upwards if the effect is inadequate. This works well when there is a risk of inconvenient weakness, such as in occupational dystonias, e.g. writer's cramp or musician's cramp. The disadvantage is that it may take sessions over 3–9 months to find the optimum compromise. In other situations the author prefers to give a fuller dose and reduce it if there are problems. This is appropriate when a more rapid effective response is needed and where undue collateral weakness is unlikely to matter, as with in spasticity in a limb unlikely to be functionally useful even if the spasticity is abolished.

GIVING THE INJECTIONS

The best sites for injection are theoretically the nerve end-plate zones deep in the muscle bulk, but these zones are not clearly mapped. They are different from the motor point, which is where the nerve enters the muscle. Fortunately, small and moderate size muscles will usually respond to BTX injected simply into the belly of the muscle. Although there is some diffusion through the muscle and fascia (Shaari et al, 1991), large muscles such as quadriceps will need separate injections for each major section. Some authorities recommend multiple scattered smaller injections to spread the toxin. Clinicians should consider the discomfort of multiple injections, and remember that an unpleasant experience may dissuade patients from undergoing

TABLE 2.
Comparison of available preparations of botulinum toxin

Preparation	Botox	Dysport	Neurobloc/Myobloc
Serotype	A	A	B
Manufacturer	Allergan Ltd (US)	Ipsen (UK)†	Elan/Athena (US)
Relative potency per mu*	3–5	1	0.01–0.02
Equivalent dose (mu)*	1	3–5	50–100
Contents of one vial	100 mu	500 mu	2500; 5000; 10 000 mu
1 nanogram toxin-haemagglutinin	20 mu	40 mu	100 (70–130) mu

adapted from Moore and Naumann (2003) * = authors' estimate; † formerly Porton and then Speywood. mu= mouse units. N.B. Dose equivalences are approximate and remain under review. Simplistic use of conversion factors can be dangerous. See text for details. Data from manufacturers.

repeat injections. Psychology can be important, and trying to get minor extra benefit may prove counterproductive.

Although electromyography (EMG) with special hollow combination EMG/injection needles can be very helpful to confirm needle placement in the chosen muscle, a simpler technique often suffices. Place the needle freehand then gently activate or stretch the muscle passively. Movement of the muscle under the skin tilts the needle and syringe and confirms its position inside the muscle fascia (Cosgrove and Graham, 1995). This is most helpful in long limb muscles, such as hamstrings, gastrocnemius and long finger flexors, and of much less use in adductors, wrist pronators and neck muscles. It can also mislead if the needle tip has passed right through the muscle. Ultrasound or other image guidance can help in some situations.

MONITOR THE RESPONSE

Establish a clear and objective baseline description of the nature and severity of any condition being treated – only then can the response be monitored. Use an established rating scale if available, such as the Toronto and Western Spasmodic Torticollis Rating Scale (Consky et al, 1990) or the Tsui (Tsui et al, 1986) scales for torticollis, which are usually sensitive to BTX-induced changes. Some conditions are much harder to monitor and the huge variety of clinical problems, even within particular indications, makes it difficult to devise satisfactory scales. Thus, Modified Ashworth Scores (MAS) may be useful in spasticity, but can only rate the impairment. They may not reflect clinically important benefit, for instance when severe poststroke fisting relaxes enough to prevent palmar trauma and skin infection, but the MAS category is unchanged. Try to agree treatment goals specific to the patient and concentrate on monitoring those goals.

The author uses a single page generic diary with a visual analogue scale for any patient where this problem is anticipated. The patient or carers can fill it in once a week. Until the pattern of response is clear, clinicians may need to see the patient 3–6 weeks after each injection, at the time of anticipated maximal response. Once everyone is satisfied of benefit such intensive monitoring becomes unnecessary, so if a pattern is established after a few sessions the author relies on patients, carers or therapists to advise when a repeat injection is needed. The author keeps completed diary forms as they give a personalized measure of baseline severity and responsiveness to BTX injections.

GIVING REPEAT INJECTIONS

Patients usually require regular repeat injections, sometimes indefinitely. Treatments can nearly always be given in outpatients, but anticipate a steadily increasing workload as patients accumulate. BTX clinics do not get smaller.

Symptom relief is generally shorter lived than objective weakness as there comes a point in the injection cycle at which the involuntary muscle overactivity becomes troublesome again. All concerned with each patient learn to anticipate this wearing off and compensate for the time lag of benefit after a repeat injection. The generic score sheets are very helpful for this. There may be pressure to repeat injections frequently. Where possible, the author tries to maintain a minimum 3-monthly interval. It is usually better to aim for incomplete but acceptable benefit than to attempt absolute control that requires excessive toxin use (see below).

FAILURE TO RESPOND

Primary biological failure to respond, with no weakness or atrophy, is extremely rare. Failure to respond clinically is usually the result of technical factors such as incorrect assessment of the clinical problem, poor muscle selection, inaccurate injections or the wrong dose. Even if the desired weakness does arise it may prove to be unhelpful, for instance when spastic muscles have additional contracture, weakening the muscle may not allow it to lengthen. Too much weakness may be counterproductive, as when a spastic knee extensor prop is abolished causing the leg to give way.

Some patients respond well at first, only to complain of a diminishing response with subsequent treatments, so-called ‘secondary failure’. Surprisingly often this is because they have forgotten the original severity of their symptoms, and the previous injection has not worn off completely. The next injection thus makes a less impressive difference, although most patients accept that they remain better than at baseline levels. Also, because injections sometimes take several weeks to work, patients complain that the reinjection has made them worse when the deterioration is in fact the result of the previous injections still wearing off. Review the original response diaries, and discuss them with the patient. When in doubt, postpone injections for a few months. Gradual decline of symptom control may persuade all concerned that BTX was helping. Sometimes coincident pathology or an increase in severity of the underlying condition overwhelm any treatment benefit. Another trap is the patient who complains at reinjection time

that the last injections are not working. Careful questioning often reveals that BTX worked perfectly well and the patient had forgotten that it is expected to wear off.

It is equally important not to persist with useless injections. BTX treatment is expensive and time-consuming, it can have side effects, and sometimes other treatments are ignored or deferred because the patient is receiving BTX. If in doubt, with the patient's consent, repeated *n*=1 trials comparing active and placebo injections may clarify whether the toxin is working or not.

ANTIBODIES TO BTX

Biological resistance to BTX may eventually develop in 2–15% of patients (Moore and Naumann, 2003), probably because they have developed neutralizing antitoxin antibodies. Antibodies seem more likely to develop in patients receiving large or very frequent doses (Greene and Fahn, 1992), so use as small a dose as will produce a clinically acceptable response and maintain a 3-month gap between injection sessions. Where patients have BTX for several indications try to give injections for all the indications in a single session to avoid multiple immunological exposures. Remember that not every indication has to be treated.

Tolerance caused by antibodies develops over a number of injection sessions so that abrupt and unexpected failure of one session may be the result of other factors, as discussed above. It is usually worth trying again, or modifying the dose and injection pattern. Laboratory tests for antibodies are not all sufficiently sensitive or specific. The author prefers to rely on clinical tests, such as the frontalis test (Hanna and Jankovic, 1998), in which BTX (50–75 mu Dysport equivalent) is injected subcutaneously into one side of the forehead. If the toxin is still biologically active the patient will develop weakness, blocking ipsilateral eyebrow elevation and forehead wrinkling. A more sensitive and quantifiable test is the extensor digitorum brevis test (Kessler and Benecke, 1997) which uses EMG of this foot muscle to assess the induced weakness. It is also less cosmetically intrusive. In practice it may be that none of these tests is worthwhile; if there is no response to maximal doses then results of special tests are irrelevant.

Patients can be switched to an antigenically distinct preparation if their response failure is caused by antibodies. There is evidence that BTXB can weaken muscles in patients with torticollis who have become resistant to BTXA (Lew et al, 1997). Theoretically, rotating or mixing serotypes may reduce the risk of antibody formation, but only a few patients develop antibodies now, and mixing or rotating BTX serotypes could just as easily increase antibody formation.

In the same vein, claims that purer BTX preparations of the same serotype are less antigenic can only be accepted as clinically valid when directly compared in controlled clinical trials. There is no proven clinical difference between the preparations currently available.

ADVERSE EFFECTS

Antitoxin cannot help in iatrogenic botulism because once the L-chains have been taken up by neurones they are no longer accessible to the antitoxin. By the time side effects are apparent, usually at least a week later, the L-chains have already damaged the vesicle-release protein machinery. Treatment of adverse events is symptomatic until natural recovery occurs.

Education is the best policy. Warn patients and family practitioners of possible side effects as some are otherwise alarming and may trigger unnecessary investigation or treatment. Tell them also that if side effects to occur it is often possible to minimize or avoid them next time by modifying the injections. The peak side effects are usually at 2–4 weeks postinjection, and adverse effects usually wear off long before the clinical benefit disappears. The same dose and pattern of injections can produce variable results, with side effects cropping up even after several apparently identical and successful injections.

Although the clinical aim is to produce a controlled and temporary focal weakness, there is commonly some spread to nearby muscles, sometimes enough to provoke more widespread local weakness. Whether this matters depends on the clinical situation. Troublesome dysphagia may follow BTX treatment for torticollis, but even quite marked unintentional weakness of hand muscles after forearm injections for spasticity may have no adverse effects in a limb which is anyway useless.

Some systemic spread occurs via the bloodstream, and sophisticated single-fibre EMG can detect subtle changes of neuromuscular junction dysfunction in distant muscles (Lange et al, 1987; Olney et al, 1988). There is no clinically detectable distant weakness at 'standard' doses, although the increasingly large doses used for suppressing spasticity may bring a risk of detectable or even troublesome systemic weakness or complaints of lethargy. Rarely, and mainly in children, distant muscles weakened by other pathology may show short-lived additional weakness such as temporary reactivation of squint or recurrence of urinary incontinence.

Systemic side effects include a flu-like illness for up to 1 week at some point in the month after an injection. Rarely, brachial neuritis has followed cervical injections. These adverse events are presumed to be immunologically mediated. Repeat injections may be trouble-free. Anaphylaxis has not been reported after many hundreds of thousands of injections worldwide.

With standard doses, probably the only dangerous adverse event encountered is dysphagia following cervical or perioral injections of BTX. It is usually mild, often no more than a feeling of a dry throat, and patients cope by taking care, sitting in an optimal posture when eating or drinking, and washing food down with a drink. In moderate dysphagia they may need to modify the diet to softer food which is more easily chewed or swallowed. In severe dysphagia the risk of aspiration with pneumonia or choking is real, and very rarely patients may need hospitalization and nasogastric feeding. One problem is the patient who derives considerable benefit from toxin injections and plays down any dysphagia, knowing that complaints may lead to lower doses and thus less benefit. The doctor can usually negotiate an acceptable compromise between benefits and adverse events.

Muscles always recover if not retreated. Uncontrolled surveillance studies have not revealed any long-term side-effects in adults or children, but neither local nor distant effects have been examined in long-term animal studies simulating the human situation of repeated sublethal doses of BTX. A few women have been inadvertently treated with BTXA during pregnancy (Scott, 1989; Calne, 1993; Moser et al, 1997). No adverse events occurred, but clearly there is inadequate experience to recommend BTXA in pregnancy. The author's own practice is to suspend BTX treatment until after delivery. If the mother is breast-feeding, the author recommends stopping for 2–3 days after BTX injection. In theory, after that time any toxin will be fixed in the tissues and is unlikely to transfer in breast milk. So far no problems have arisen.

RUNNING A BOTULINUM TOXIN SERVICE

Many BTX clinics have developed piecemeal, run by interested specialists as part of their wider service. Ophthalmologists and neurologists were the first to exploit BTX and run clinics in most major cities. The range of specialties now using BTX in other fields has led to diverse clinic profiles, and clinicians who are setting up new clinics should review the options and adapt to their local circumstances. There are a variety of points that affect most services:

- The cost of BTX has led many clinicians to use it in a dedicated service to minimize waste.
- BTX clinics rarely get smaller. Local demand is likely to grow, and as most of the disorders treated require regular repeat treatments, clinicians can rapidly find themselves spending more time and resources running a BTX service. It is essential to plan for this, and especially to establish systems to cope with the workload and the costs.
- Where appropriate, guidelines advise using BTX in the context of a wider clinical service. Good examples are management of adult spasticity with BTX in the setting of a rehabilitation unit with a multidisciplinary approach (Barnes et al, 2001), or childhood spasticity in a child development centre with access to neurology, orthopaedics, physiotherapy and orthotics (Graham et al, 2000).
- Users must have appropriate general training in their speciality and specific training in the use of BTX. General training includes understanding the diagnosis and differential diagnosis, investigations and choice of treatment. Specific training should cover the pharmacology, physiology, biochemistry, benefits and adverse effects of BTX, relevant dynamic anatomy, short- and long-term strategies for using BTX, monitoring outcomes, and when to stop treatment. There are specific training guidelines in some situations (Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, 1994).
- Some conditions are straightforward to treat, and suitably trained delegates can be effective and safe. It does not always have to be the doctor giving the injections, although doctors are advised to monitor delegates closely. UK clinics are using specialist nurse practitioners to deliver some BTX treatments and randomized controlled trials have shown that, for selected patients, this practice is effective and safe as a home care service (Whitaker et al, 2001), and in a hospital-based clinic (A Moore, D Rog, unpublished data, 2002).

THE WIDER MEDICAL INFLUENCE OF BOTULINUM TOXINS

The rapidly expanding potential of BTX has galvanized medicine in several other ways. It has provided an intellectual and financial stimulus, opening up a wide variety of fields. BTX has clarified our understanding of the aetiology and pathophysiology of diseases such as dystonia and spasticity. It is not so long ago that many

clinicians considered dystonia to be a non-organic disease; successful treatment with BTXA helped to confirm dystonia as a physical rather than a psychiatric illness. Many patients remain extremely grateful for their new classification. Experiments on patients treated with BTXA have yielded fascinating insights into the underlying neural mechanisms of dystonia and spasticity (Hallett, 2000).

The financial muscle of the pharmaceutical industry has been drawn to these new fields and supports both basic and clinical research. Early investigators used science, imagination and intuition to broaden the scope of treatment with BTX, to generate and test hypotheses in often small and uncontrolled studies. Their enthusiasm, combined with the discipline imposed by drug regulatory authorities, led to more definitive randomized controlled trials. For some disorders BTX was the first treatment subjected to this scrutiny, and this triggered re-evaluation of many older treatments. The challenge of rolling BTX out from research settings to routine use in health services has stimulated reviews and revision of much wider aspects of these services, especially for dystonia, spasticity and rehabilitation medicine, and generated debate about the ethics of cosmetic uses of BTX.

As we understand more about the ways BTX works, we will be able to improve techniques for treating current indications, and probably develop new indications. Even more exciting is that scientists are developing hybrid molecules that may target L-chains to new cells, or use H-chains to direct new therapeutic moieties to cholinergic neurones. There are many possibilities. **HM**

Conflict of interest: The various manufacturers of botulinum toxin have paid the author for advice, for assistance with education and for speaking at meetings. They have supported research at his university unit.

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KEY POINTS

- Many different specialties now use botulinum toxin for a wide range of conditions that are characterized by focal muscle or autonomic glandular overactivity. Many uses are still off-licence.
- In therapeutic doses botulinum toxin causes focal muscle weakening or suppression of autonomic glandular function, by blocking acetylcholine release.
- Used properly it is generally safe, with no identified long-term adverse effects. Short-term adverse effects are caused by excessive local weakness.
- Users should undergo specific training, but botulinum toxin is usually a straightforward treatment given in outpatients.