Spasticity Treatment with Botulinum Toxin

Botulinum Toksin ile Spastisite Tedavisi

Anthony B. WARD
North Staffordshire Rehabilitation Centre, Burslem, United Kingdom

Summary

Spasticity is a physiological consequence of an insult to the brain or spinal cord, which can lead to life-threatening, disabling and costly consequences. This typically occurs in the patients following stroke, brain injury, spinal cord injury, multiple sclerosis and other disabling neurological diseases and cerebral palsy. Its current management has been advanced considerably over the last ten years by new thinking and by new drugs and technology. The sole indication for treating spasticity is when it is causing harm. Physical management (good nursing care, physiotherapy, occupational therapy) through postural management, exercise, stretching and strengthening of limbs, splinting and pain relief are the basis of spasticity management. The aim of treatment in all cases is to reduce abnormal sensory inputs, in order to decrease excessive and uncontrolled alpha-motor neuron activity. *Turk J Phys Med Rehab 2007; 53 Suppl 2: 6-12.*
Key Words: Spasticity, management, botulinum toxin

Özet

Spastisite beyin ve spinal kord hasarı sonrası görülen, hayatı tehdit eden, sakatlığa yol açan ve maliyeti arttıran fizyolojik bir sonuçtur. Spastisite tipik olaraki inme, kafa travması, spinal kord yaralanması, multiple skleroz, diğer sakat bırakıcı nörolojik hastalıklar ve serebral palsi geçiren hastalarda görülür. Son on yılda yeni düşünceler, yeni ilaçlar ve teknolojiler sayesinde spastisite tedavisinde gelişmeler kaydedilmiştir. Eğer spastisite zarar veriyorsa tedavi endikedir. Fiziksel tedavi (iyi bakım, fizyoterapi, iş uğraş tedavisi), postural tedavi, egzersiz, germe ve kuvvetlendirme, cihazlama ve ağrının giderilmesi spastisite tedavisinin temelini oluşturur. Tüm olgularda tedavinin amacı anormal duyusal girdileri azaltarak, aşırı ve kontrolsüz alfa motor nöron aktivitesini düşürmektir. *Türk Fiz Tıp Rehab Derg 2007; 53 Özel Sayı 2: 6-12.*
Anahtar Kelimeler: Spastisite, tedavi, botulinum toksin

Introduction

Spasticity is a physiological consequence of an insult to the brain or spinal cord, which can lead to life-threatening, disabling and costly consequences. This typically occurs in the following patients following stroke, brain injury (trauma and other causes, e.g. anoxia, post-neurosurgery), spinal cord injury, multiple sclerosis and other disabling neurological diseases and cerebral palsy. Its current management has been advanced considerably over the last ten years by new thinking and by new drugs and technology. Lance's definition (1) of 1980 is still relevant and the impairment is classified as one of the movement disorders. It is important therefore to stress when teaching on this topic, in order to highlight the need for patients' spasticity to be assessed while they are functioning. The fact that many attempts have been made to define it shows the degree of its complexity, but Young (2) described spasticity as part of the upper motor neuron syndrome and gave a definition as "a velocity-dependent increase in muscle tone with exaggerated tendon jerks resulting in hyper-excitability of the stretch reflex in association with other features of the upper motor neuron syndrome".

He also described spastic dystonia and spastic paresis, which are somewhat contentious terms, but do highlight the positive and negative features of the upper motor neurone syndrome and these are set out in Table 1. Essentially, if left untreated following damage to brain or spinal cord, it is characterised by muscle overactivity and high tone spasms and will lead to muscle and soft tissue contracture.

Applying this definition to patients in clinical settings has been difficult because upper motor neuron lesions produce and array of responses. The pattern depends on the age and onset of the lesion, its location and size. Patients with diffuse lesions

Address for Correspondence: Dr. Anthony B. Ward, North Staffordshire Rehabilitation Centre, The Haywood, High Lane, Burslem, Stoke on Trent ST6 7AG, United Kingdom
Phone: 0044 (0)1782 556 226 Fax: 00 441 782 556 165 E-mail: Anthony.Ward@uhns.nhs.uk **Accepted:** October 2007

produce, for instance, different characteristics to those with localised pathology and the speed of onset changes this again (3). More recently, the SPASM Consortium in Newcastle-upon-Tyne, UK has tried to adapt the accepted definition to a more practical base and make it more relevant to clinical practice and to clinical research (4). Its definition is thus as follows.

• Assuming that all involuntary activity involves reflexes, spasticity is an intermittent or sustained involuntary hyperactivity of a skeletal muscle associated with an upper motor neurone lesion.

It takes as read, that there are a number of different syndromes seen following an injury to the brain of spinal cord and that the assessment and management of spasticity is one of a number of events that occurs. Its treatment should be planned whatever the other features of the upper motor neurone syndrome.

Spasticity is also frequently classified by its presentation and divided into generalised, multifocal and focal. The term, focal spasticity, is imprecise, for it is not the spasticity that is focal, but that spasticity is producing a focal problem that may be treated by local means. In this respect, botulinum toxin is one of the pharmacological interventions of first choice and some aspects of its application will be discussed below. In addition, its place in the overall management of spasticity will be discussed in this paper, which looks more at the practicalities of its administration than the science behind them.

2. Management Principles

The sole indication for treating spasticity is when it is causing harm. Successful treatment strategies have now been developed and there is good evidence of treatment effectiveness. Physical management (good nursing care, physiotherapy, occupational therapy) through postural management, exercise, stretching and strengthening of limbs, splinting and pain relief are the basis of spasticity management (5). The aim of treatment in all cases is to reduce abnormal sensory inputs, in order to decrease excessive and uncontrolled α-motor neuron activity (6). All pharmacological interventions are adjunctive to a programme of physical intervention and there is a good evidence base for this in relation to botulinum toxin treatment (7). Stretching plays an important part in physical management, but needs to be applied for several hours per day (8). This would of course be impossible to do on a one-to-one basis with a therapist and limb casting has merits in getting around this difficulty. It can thus provide a prolonged stretch of a limb (9).

Newer technologies, such as botulinum toxin, demand greater specificity of the aims of treatment. All the members of the rehabilitation team, including the patients and family/carer, have to be clear about what is trying to be achieved. It is also important that all the members of the treating team have the same expectations of the outcome, so that they give consistent message to the patient and carer. To achieve this a management strategy is adopted (Figure 1), which shows the treatment principles adopted in specialist units.

Table 1. Upper motor neurone symptoms.

Positive	Negative
Muscle tone	Paresis
Tendon jerks	Loss of fine control
Repetitive stretch reflexes (clonus)	Loss of dexterity
Extensor stretch reflexes	Fatiguability
Released flexor reflexes	Early hypotonia
(Babinski, mass synergy pattern)	

Successful spasticity management is a multi-professional activity. Any underlying provocative factors (such as poor posture, constipation, incontinence, limb pain, skin or tissue damage) should initially be addressed. If further more active management is required, the team can then discuss with the patient and carer the available options. Some will be physical treatments and some will be pharmacological or medical/surgical interventions. A management plan is therefore devised for each patient. Management is not a question moving from one treatment to another when the first fails. Patients should be exposed to the appropriate choice of treatments to meet their needs.

2.1- Planning Treatment

It is important to develop a formal treatment plan in order to document the intended outcomes. These should be written and agreed with the patient. To reiterate, the underlying principles are that:

• Antispastic drugs treat spasticity. They do not treat contractures and they will not make hemiplegic limbs function, unless the patient's function is impeded by the spasticity.

• The management of spasticity is physical and all pharmacological interventions are adjunctive to that.

With this in mind, the treatment plan follows a standard pathway:

2.2- Patient Assessment

Spasticity is a movement disorder and patients cannot be adequately assessed unless they are observed during movement and function. Physiotherapists and occupational therapists contribute greatly to the observation and examination process, but some patients with complex movement patterns need assessing in a gait laboratory. The assessment process highlights the differences in patterns of limb posture and movement following an upper motor neuron lesion. Where there is no movement, the assessment process is fairly straightforward, but

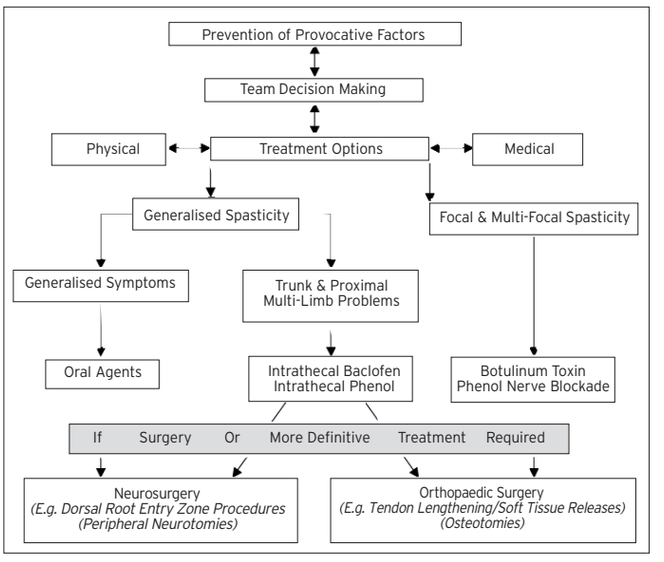

Figure 1. Proposed management strategy (11,12).

where there is loss of motor control rather than a spastic dystonia, one has to attempt to identify the different aspects of motor impairment. Patients with longstanding problems also develop compensatory methods of movement, which may or may not require treatment and the clinician has to be clear about the underlying pathophysiological processes.

It is then possible to identify how function is impaired and whether the problem is generalised, multi-focal or focal. This will then point to the options for treatment, but, if botulinum toxin (BoNT) is planned, then more specific detail is required about which muscles are contributing to the functional impairment. The clinician therefore has to learn about functional anatomy as well as surface anatomy, when therapeutic injections are planned. Traditionally, BoNT has not been used early on following a stroke or brain injury, but there is now evidence of its safety even within a few days of the event and while the patient remains in the intensive care unit (10).

2.3- Defining the Aims of Treatment

Care pathways are recommended for linking with patients' individual programmes of rehabilitation. As spasticity covers a range of clinical scenarios, it is tempting to use BoNT in a random manner, which may thus diminish its value. Although there are a wide number of reasons to treat spasticity with antispastic drugs and botulinum toxin in particular, the actual indications are quite specific and clinicians should follow these closely (11) Patients may fulfill more than one indication, e.g. pain relief and care management, but it is inappropriate to give BoNT simply "to see its effect".

The five indications are thus:

In essence the assessment process for BoNT treatment aims to answer the following questions:

Botulinum toxin is effective in reducing muscle hypertonia and is associated with functional improvements (13). It can also be used with other treatments and the Tables 2, 3 and 4 below highlight some of the issues with planning treatment and choosing the right drug.

3. Treatment with Botulinum Toxins

3.1- How Do Botulinum Toxins Work in Spasticity?

BoNT is injected into overactive target muscles, which are responsible for involved in the clinical picture. It is a potent neurotoxin, that inhibits the release of neurotransmitter chemicals by disrupting the functioning of the SNARE complex required for exocytosis of synaptic vesicles (14). Its characteristics mean that it very suited to long term blocking neuromuscular transmission through acetyl choline release inhibition. This causes muscle paralysis over three to four months, but this can be extended by a programme of physical activity. The toxin will cross about four to five sarcomeres to get to the neuromuscular junction and can be seen there after about 12 hours. It is also seen in the anterior horn cell at about 24 hours, but does not exert an influence there, unlike tetanus toxin (15). The toxin's clinical effect is seen at about 4 days and is certainly working at seven days. It works optimally at one month and will go to produce a clinical effect for three to four months. The actual molecular mechanism of its action will not be addressed here in any detail, as there are several texts better able to describe this (16). The end effect is weakening and relation of muscle overactivity in people suffering the effects of the upper motor neurone syndrome. This results in a biomechanical change in the muscle's function and makes it amenable to stretching and

Table 2. Indications for antispastic treatment.

Indication	Example
Functional improvement	Mobility: enhance speed, quality or endurance of gait or wheelchair propulsion Improve transfers Improve dexterity and reaching Ease sexual functioning
Symptom relief	Relieve pain and muscle spasms Allow wearing of splints/orthoses Promote hygiene Prevent contractures
Postural improvement	Enhance body image
Decrease carer burden	Help with dressing Improve care & hygiene Positioning for feeding, etc.
Enhance service responses	Prevent need for unnecessary medication & other treatments Facilitate therapy Delay or prevent surgery

Table 3. Patient selection checklist (12).

What are the problems and will BoNT help?
Is there a significant component of muscle overactivity to treat effectively with BoNT?
Is the problem localised to a number of muscles?
Is there a clear aim for treatment?
Are the advantages of BoNT treatment clear?
Are there any contraindications to BoNT injection?
How will treatment outcomes be evaluated and are there appropriate measures to use?

lengthening. In addition, the weakening allows an opportunity to strengthening antagonist muscles and thereby restore some of the balance between the two.

3.2- Evidence for the Use of Botulinum Toxin in Spasticity

There are many publications supporting the scientific basis for using BoNT in spasticity management, particularly at an impairment level (17, 18). In most randomised controlled trials, the effects of BoNT are compared with placebo over a single injection cycle. The outcomes are generally positive and support the use of the drug, but they do not necessarily reflect what is important in clinical practice. In addition, data from RCTs are less convincing than those from open studies for a variety of technical reasons, which is perhaps reflects the difficulties in finding good outcome measures for spastic patients (19). Clinical experience tells us that BoNT can reduce spasticity and improve voluntary movement and active function in selected patients. Again, RCTs have had difficulty showing active functional improvement, despite the clear ability of BoNT to reduce spasticity and this is, to a large extent, due to poor methodology, especially in patient selection and injection protocols and the choice of outcome measures. Motor dysfunction is usually caused by weakness (and other "negative" features of upper motor neurone syndrome) rather than by muscle overactivity. Clinical trials therefore need to take this into account in designing trials (20, 21).

There is good evidence that BoNT has clinical benefit in treating the mechanical effects of spasticity. Future research strategies should now concentrate on its longer-term use, the as yet unresolved technical issues of how to get the best out of this new treatment and, of course, its cost-effectiveness. Brashear, et al showed very well the benefits of BoNT over a twelve-week cycle in terms of Ashworth score, Disability Assessment score and patient and physician global rating scale (13). Of the 126 patients (64 in the treatment group and 62 in the placebo group), 122 completed the study. 111 of these patients then entered an open-label phase and were followed up for 42 weeks (22). This was the first long-term study of BoNT in a stroke population. One patient did not receive BoNT and the 110, who did, carried on treatment under clinical conditions. They had up to four further treatments and the value of this study is clear. 110 were entered for the first cycle, 96 were entered for the second, 81 for the third and 26 for the fourth. Firstly, there were significant improvements from baseline across all the measures at each treatment cycle and this remained constant, whether the patient was injected only once or four times. Secondly, there was considerable variation in the length of response to the injection and a beneficial effect lasted for over 24 weeks in 7.4% of patients. The average number of treatments was 2.72 in this 42-week period. Overall, the patients were observed for 54 weeks and the safety profile of the drug remained, no matter how many treatments were given. This not only supports previous short-term work (23-25), but sets the scene for further long term studies to look more at the overall impact on patients' activity, functioning and participation, as well as on the impact to service provision.

There has been some work in studying the combination of BoNT and physical treatments, but most have run into problems standardising treatments. However, some have produced evidence to show the increased benefit of BoNT to the physical management of spasticity. Muscle stretching may improve the therapeutic effect of BoNT and vice versa (26), but this needs to be established in a RCT. Standing and walking have improved following BoNT (27,28). BoNT was compared to casting and to standard physiotherapy within a few days of a brain injury. Active treatment (BoNT › casting) had a better outcome than standard treatment and there were no adverse events in the BoNT patient group (10). Biomechanical changes may thus be prevented in the longer term by treating patients enthusiastically at such an early stage. Further studies will need to be done to show these benefits in functional terms, but BoNT and casting in combination has real potential

There is now evidence for the effect of BoNT in all acute and chronic spastic conditions and the common thread is that the drug has a peripheral action, thereby negating the differences

Table 4. Current proven effective treatments.

Treatment	Value	Problems
Oral agents	Baclofen & Dantrolene - cheap. Tizanidine – seven times cost of baclofen Gabapentin, Pregabalin	40% of patients unable either to tolerate oral agents because of side-effects or unable to produce an adequate antispastic effect before side-effects occur
Botulinum toxin	Effective for focal spasticity Simple to prescribe Simple intramuscular injection Need trained clinician to treat	Seen as expensive, but good value over the four-month effect of the drug. Budgetary limits. Reversible effects. Considerable benefit to management
Phenol nerve & motor point block	Cheap drug Time consuming to give	Expensive to give in clinical time. Painful to give. Potential for severe complications
Intrathecal baclofen	Expensive hardware Eight to ten year life	Need for prolonged inpatient assessment required. Requires patient compliance and education. Need proper contract to deal with pump renewals
Intrathecal phenol	Lumbar puncture required, but straightforward treatment in comparison to intrathecal baclofen. Cheap product.	Only for very severely disabled patients with limited physical (and possibly cognitive) function, limited life expectancy. Must be incontinent.
Surgery	Neurosurgical & orthopaedic procedures. Expensive, but valuable. Limited indications and patients	Painful, irreversible, invasive Variable results & effectiveness. Paraesthesiae, bowel/bladder changes

effects of the aetiology. In summary, it is now certain that BoNT does reduce spasticity, as measured by the Ashworth score, pain, spasms and the symptoms associated with all of these. These include some local functional goals, such as hygiene and relieving carer burden for dressing, positioning, etc, as measured by the Disability Assessment score. One of the real beneficial aspects of BoNT is its safety profile and all of the RCTs and open studies make specific comment on this. Adverse events are small in number and only minor. Even in very ill patients, it was safe and it also contributed to a protective effect of anti-spastic treatment in preventing the immediate effects of limb deformity early on after severe brain injury (10).

Collecting evidence for the effectiveness of BoNT in managing spasticity is necessary (12) and the UK Department of Health recently called for applications for a longer-term study of the effectiveness and cost-effectiveness of BoNT in post-stroke spasticity. Studies are currently underway to demonstrate the place of the drug in comparison to oral agents in stroke and brain injury and this correlates with the reality of physicians making the choice between these two treatment strategies for their patients. This placebo-controlled double-blind study of BoNT vs. tizanidine vs. placebo tablets and placebo injection will attempt to define a strategy for antispastic treatment early on in stroke and brain injury rehabilitation. This also needs to be done for chronic neurological disease to support the initial attempt by Hyman, et al. (29).

3.3- Muscle Location

Electromyography & Muscle Stimulation

The use of EMG guidance and muscle stimulation is generally favoured to locate muscles accurately for injection. This is not necessary for large, superficial, easily visible muscles, but is advisable for smaller and deep muscles and particularly applies to forearm and lower leg muscles, hip flexors (psoas major) and small inaccessible muscles around the jaw. The aim is to record muscle action potentials and their interference pattern on muscular activation. This can sometimes be difficult to interpret in view of mass synergies in spasticity and either active contraction of the muscle or passive movements will inform the injector of correct placement. EMG guidance is particularly useful in flexor digitorum profundus and extensor digitorum communis muscles, which are organised in muscular fascicles supplying each digit. Correct placement of the needle can therefore allow neuromuscular blockade for each fascicle and thereby a very accurate result. Observing muscle action potentials makes that one is sure that the needle is in a muscle, but cannot always correctly identify which muscle. This is particularly so in small muscles. The combination of this, therefore, with muscle stimulation makes for a more accurate assessment and gives the injector confidence of the actual location of the needle (RDG stimulator).

The procedure is carried out using a hollow Teflon-coated EMG needle with a sideport for syringe attachment. Motor point stimulation can also be carried out to activate small intramuscular fascicles, but this is time-consuming. Its advantage, however, is that it places the toxin as closely as possible to the motor end plate, the binding area, but increased effectiveness has not been shown in human studies. Animal studies would support a relationship between dose-related diffusion and the muscle response (30) and it is now important to study humans. At the present time the avid binding of toxin to presynaptic nerve terminal would not necessarily make this vital for clinical practice. Motor stimulation has been used primarily for nerve blockade and the immediate expected response can authenticate the accuracy of the procedure. It is possible that accurate localisation through EMG guidance can reduce the dose of toxin. This is obviously important for patients with progressive disorders, such as multiple sclerosis and for patients requiring repeated injections. In this way, costs will be contained and the chance of antibody-mediated non-responsiveness will be decreased. Again there is no direct evidence of this and opinions for and against the technique have been based on a small number of patients in an uncontrolled situation (31,32). However, motor point injection with phenol takes longer to do and the increased procedure time taken should be included in the comparison of costs.

Computerised Tomography & Ultrasonography

Routine use of computerised tomographic (CT) radiography location of muscles is not justifiable from a safety point of view in view of the accuracy of the above techniques. Ultrasound, on the other hand, has a useful place in locating both superficial and deep muscles and is growing in usage. It is safe, non-invasive and does not distress patients. It is accurate, but does require the injector to learn the technique and to orientate him or herself to the expected findings. Alternately, an ultrasonographer is required, which increases both the cost and technical organisation of the procedure. Although ultrasound machines are costly, reasonable arrangements can be achieved through rental and leasing contracts.

3.4- Post-Injection Care

The treatment of spasticity is enhanced by a programme of physical treatment after BoNT injections or nerve blockade (33) and physiotherapy in the form of stretching and strengthening is thus required for a period following the procedure. It has also been noted anecdotally, that the effect of a single dose of BoNT-A can be prolonged beyond its action duration and repeat injections, which are necessary for MS patients can be reduced to a minimum. Limbs should be stretched to a functional position, but should not be traumatised, as this will provide a nociceptive stimulus to increase spasticity in non-injected muscles. Therapy should be given every day for a period of at least four weeks, but the benefit, duration and optimal regimen require scientific evaluation. Similarly, there is anecdotal information, that, to be effective, stretching should be carried out for several hours every day. Clearly, this cannot be done on a one-to-one basis and splinting/casting can provide a stretch for several hours. Occupational therapists have taken responsibility for this treatment. Night resting casts are particularly valuable, as they achieve this purpose, but do not interfere with daily activities.

Follow-up is important to identify whether or not the treatment objectives have been met and to plan further treatment. As has been stated above, it is important to identify those muscles requiring injection at the start of the treatment episode and to re-inject three to four months, if necessary, after the first. At each follow up, the relevant outcome measures should be recorded and it is worth having a separate page in the clinical notes for this purpose, noting the date of the injection, the muscles injected and the outcome measures used. Multiple

sclerosis patients, like others with chronic spasticity, may require repeated injections and it is important to have at a glance clear documentation of what has been previously done. A trend may thus be observed to aid further management. Good documentation is important to make the best of follow up assessments and an example is described in the Royal College of Physicians Guidelines (12).

3.5. Organisation of Services for Botulinum Toxin Treatment in Spasticity.

The optimal configuration of services will vary in different places, and flexibility is important. They will usually revolve around specialist rehabilitation units, neurology or stroke services or departments of medicine for the elderly. Requirements include:

I. Clinician(s) trained in spasticity management in general, with specific additional training in botulinum toxin treatment. This is probably best achieved by a combination of specific courses and apprenticeships with direct instruction and supervised practice.

II. An active physiotherapy and OT service, with roles in selecting patients for treatment and arranging or delivering targeted physiotherapy after injection, and ensuring appropriate provision of orthoses. There should be good links with physical therapy departments in referring units elsewhere.

III. Orthopaedic advice should be available.

IV. Many injections can be performed in dedicated outpatient clinics. These allow more convenient and cost-effective assessment and follow-up by multidisciplinary teams, minimal wastage of BoNT, and easier access to equipment such as EMG to help with injections, plus availability of nursing staff trained to assist in the sometimes awkward patient manoeuvring required.

V. A ward or even a roaming service may be needed: many patients with spasticity are difficult to transfer to a clinic. A portable EMG device may be required

VI. Services should consider avoiding or minimising the use of more than one of the available BoNT preparations in order to avoid the risk of confusion over doses.

VII. Many patients like to have their next appointment for review and usually treatment at a pre-arranged interval, especially if their response is fairly predictable. Those with an unpredictable or long-lasting response may prefer self-referral when their last injections are wearing off. BoNT clinics should attempt to accommodate both: although patient-initiated appointments may be difficult to fit in, this strategy generally acts to reduce the number of injection sessions.

VIII. A clearly defined mechanism for paying for the toxin and the service. Ad hoc arrangements can be financially risky for host institutions.

4. Conclusion

The contribution of BoNT in spasticity management is now well recognised. The trick in clinical management is to use it wisely and know when and when not to use it. Table 5 highlights some of the advantages and disadvantages.

It must be remembered that BoNT is a useful short-term means of improving patients' function and the distressing features of spasticity. This is against the background of a long term condition, for which a long term management strategy is required.

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Table 5. Advantages and disadvantages with BoNT treatment.

Advantages	Disadvantages
• Efficacy whatever cause of spasticity • Effectively treats focal problems • Specific treatment • Very safe drug – reversible effects • Easy to use • May reduce need for systemic drugs • Few drug interactions • Role in prevention	• Cannot treat widespread spasticity • Requires a combined approach • Reversible, needs repeating • Not a long-term solution • Difficult to estimate cost-effectiveness • Assessment of muscles to be injected can be difficult • Potential cost implications

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