We initiate the therapy with 100 mg daily. We may increase the dosage to 200 mg daily. We administer the medication in the morning. If a second daily dose is required, it is administered before 1:00 PM to prevent adversely impacting nocturnal sleep. Interference with BCPs may necessitate use of alternative forms of birth control. It is generally well tolerated. The most commonly reported side effects include transient headache and nausea.

Fatigue is present in many diseases associated with transverse myelopathy. There is data about fatigue in MS, but there is not data about fatigue associated with TM. There are many different kinds of fatigue. When we treat fatigue, we need to identify the specific type of fatigue we are treating. Measuring fatigue is an inexact science; the measures are very subjective. Lassitude, the most common and significant fatigue in MS, remains a bit of a mystery. It must have a neurochemical basis. There are treatments for fatigue. It is difficult to manage, but with a team approach and the three P’s, physical, psychological, and pharmacological therapies, we can, in fact, help most people who have fatigue with neurologic disease.

Spasticity Management
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Kennedy Krieger Institute

Adapted from a presentation given at the 2006 Rare Neuroimmunologic Symposium
The treatment of tight muscle by stretching has been practiced in many cultures as far back in time as the ancient Roman Empire. This basic technique is the cornerstone for the management of spasticity.

This chart identifies the different types and levels of intervention in cerebral palsy. These concepts can also be applied to individuals with spasticity of spinal cord origin. It is an algorithm that describes how treatment decisions might be made. Different approaches may be tried at different times, depending on the condition of the patient. Treatments may be divided into rehabilitative interventions, which include physical and occupational therapy, medical interventions, which include therapeutic botulinum toxin injections, oral medications, and surgical interventions. Surgical interventions include orthopedic surgery, which have been the mainstay over the years for treating joint contractures (a complication of spasticity); dorsal rhizotomy, which is a neuro-surgical procedure that decreases the sensory stimulation to the nervous system; and intrathecal Baclofen pump placement. This last intervention is a surgical procedure in which a programmable pump is placed into the back and then a flexible catheter slowly infuses the medication, Baclofen, directly into the cerebral spinal fluid.

Spasticity is treated because it causes pain and limits the function of the musculoskeletal system. Increased comfort allows more freedom of movement and access to the environment. In addition, spasticity treatment can improve arm and leg movements and allow performance of crucial activities of daily living (ADLs) like dressing, cleaning, eating and hygiene. Treating spasticity may make it easier to wear braces. For example, a plastic ankle foot brace which is also known as an AFO (ankle foot orthosis) may cause blistering or redness, because the foot is being forced down by spastic calf muscles. Treating these muscles to reduce spasticity makes it possible to wear the AFOs for standing or walking. Another reason to treat spasticity is for the evaluation of the effects of potential orthopedic surgery designed to realign joints that have been affected by the unrelenting pull of tight muscles. In some cases it may postpone surgery, reduce the amount of surgical correction needed, or prevent surgery. The issue of timing of

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Table 1: Cerebral Palsy Treatment Algorithm (courtesy of Alexander Hoon, MD)
surgical intervention is of special concern in children, because of the effects of spastic muscles on growing bone.

Early in the course of spasticity, a joint and the spastic muscles attached to it may be relatively flexible. Over time the amount of movement possible at a joint decreases and function is lost. At this point, a contracture has developed and surgical intervention may be the only way to regain the full range of motion at that joint. Intervening aggressively before this happens with a consistent and appropriate therapy and stretching program augmented by medications, injections, physical modalities like heat or cold, braces, and serial casts is important.

If normal muscle stretching does not occur, then a joint contracture develops. The familiar phrase: “If you don’t use it, you lose it” definitely applies. If muscles aren’t stretched to their full range of motion, they will physically shorten and lose structural elements called sarcomeres. In other words they shrink. Fortunately, muscles can also add sarcomeres, if they are gradually and carefully stretched. Many rehabilitation techniques and interventions are directed toward improving the length of contracted spastic muscles.

There are two different kinds of contractures. Dynamic contractures that occur during movement and fixed contractures that are present at all times. Unfortunately, progression from dynamic to fixed contractures is difficult to prevent. A dynamic contracture is noticed when an individual is trying to use a muscle to move a limb. A good example would be walking on the toes or extending the arm when trying to reach for an object.

Examples of abnormal positions or movements in individuals who have spasticity include “equinovarus” which is an inward movement of the foot toward the midline plus toe walking, and “striatal toe” which is an up-going toe from over activity of the muscle that pulls the toe up. “Stiff knee” gait (also called a “compass” gait) occurs from over activity of the quadriceps muscle, “crouch knee” gait that is the result of hamstring dynamic contractures, and “scissoring” from hip adductor muscle dynamic contractures. In the upper extremities, spasticity can cause finger, wrist, elbow, and shoulder flexion contractures. These can occur alone or in combination to interfere with fine motor tasks such as eating, dressing, and hygiene.

Surgical lengthening of muscle contractures can be performed, if the limitation of motion is interfering with functional tasks. If surgery is being considered, it is essential to clearly identify the goals, discuss all the potential complications with the surgeon, plan for post-surgery rehabilitation, and consider the effects of surgery on the entire family.

One way to look at interventions for treating spasticity is to think about interventions in terms of being either general or focal and either reversible or permanent.

This table is divided into four quadrants. The upper left hand quadrant describes interventions that work on the body as a whole (general), and are reversible. A good example of this is oral medications. This is in contrast to interventions in the upper right hand quadrant which are general, but not reversible. An example of this type of intervention is a selective dorsal rhizotomy which is a surgical procedure in which nerves that affect spasticity are cut just before they enter the spinal cord. This will change the muscle tone of muscles in the lower limbs, depending on how many nerves are cut. The bottom half of the diagram represents interventions directed at specific target muscles (focal treatments). Local corrective orthopedic surgery would be an example of a focal intervention that is permanent. A reversible and focal intervention is chemo-denervation which is currently most commonly done by injecting either botulinum toxin in very small amounts or phenol into targeted spastic muscles with the intent to temporarily weaken those muscles to improve the effectiveness of therapy.

Botulinum toxin injections for therapeutic purposes have been performed for about 15 years, since the early 1990s. Historically, the presence of a biological toxin was first suspected in the early 1800’s by Justinus Kerner who investigated “sausage poisoning.” The bacteria Clostridium botulinum, from which botulinum toxin type A was eventually purified, was first identified as a causative agent in food poisoning more than 100 years ago (1895) in Ellezelles, Belgium, by Professor Emile Pierre van Ermengem. It was purified by Dr. Schantz in 1944 and in

<table>
<thead>
<tr>
<th>General</th>
<th>Reversible</th>
<th>Oral medications</th>
<th>Selective dorsal rhizotomy</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>Chemo-denervation</td>
<td>Local corrective surgery</td>
<td></td>
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Table 2: Surgical and Pharmacologic Treatments (Modified from Graham HK, et al. Gait Posture. 2000).
1968 Dr. Scott, an ophthalmologist, came up with the idea of using it for medical reasons. Interestingly, the first indications were for treating muscles around the eye that caused uncontrollable eye blinking or blepharospasm and to treat strabismus which is a condition where the eye muscles are not in balance.

The bacteria that causes botulism is *Clostridium botulinum* which is a gram positive anaerobic rod type of bacteria. It produces an exotoxin which blocks the release of acetylcholine molecules at the site where the nerve that controls muscle contractions is connected to individual muscle fibers. Acetylcholine molecules act as neurotransmitters which activate muscles. Botulinum molecules block the release of acetylcholine from vesicles that store up these molecules in the nerves. *Clostridium botulinum* produces eight different kinds of neurotoxin of which only two, type A and type B, are used for chemo-denervation.

The effect of the botulinum toxin molecule on the nerve ending is reversible. The botulinum neurotoxin doesn’t kill the nerves; it temporarily shuts it off.

Perhaps the most important question in the management of spasticity with injections of botulinum toxin or other interventions is to decide upon the specific goals for treatment. Before giving a botulinum toxin treatment, it is important to have agreement between the patient and their family, physicians, and therapists as to the expectations for what the botulinum toxin is going to do so that unrealistic expectations are avoided.

When examining someone for botulinum toxin injections, it is important to determine if limited range of motion is due to spasticity or to muscle tightness from fixed contractures. At the end of a muscle stretch, is there a “hard” or a “soft” end point. The “hard” end point goes along with a fixed contracture that would not benefit from botulinum toxin treatment and a “soft” end point would suggest that chemo-denervation should be considered. A “catch” during the stretch of a tight muscle is another sign of a spastic muscle rather than a contracted muscle. In addition, the more time that joint motion has been limited by spasticity, the greater is the chance that there is a fixed contracture present that would not respond to botulinum toxin treatment.

The distribution of the affected muscles is another consideration in the decision to treat with botulinum toxin. A focal intervention like botulinum toxin is most useful when a beneficial effect from selectively weakening specific muscles around a joint can be identified. For example, muscles that flex the elbow may be overactive and prevent the individual from reaching out for an object. If the elbow flex or muscles, especially the biceps are weakened, then the therapist can stretch out the biceps, extend the elbow, and potentially improve reaching for objects.

Sometimes a botulinum toxin injection is used to decide whether a permanent focal intervention like orthopedic surgery would be of benefit. A good example of this would be treating tight calf muscles that cause toe walking. If there is a good effect from the botulinum toxin in terms of bringing the heel down to the ground thus allowing walking with flat foot, then a surgical lengthening of the calf muscles may be considered.

If a patient has muscle tone that is severe and spread throughout the body, then botulinum toxin may not be a good intervention, because there is a limit to how many muscles you can inject. However, if certain key muscles can be injected that would result in an identifiable benefit for the patient, such as relief of pain, then botulinum toxin may be considered.

Some general facts about botulinum toxin are as follows. The usual onset of action is 12 to 72 hours after treatment, depending on the size of the muscle and the dose of botulinum toxin that is administered. The time to peak effect is about seven to ten days. This also could vary from patient to patient. The average duration of response is about one to six months with an average of three months. This is also variable and depends upon the amount of spasticity versus contracture in the target muscle and the patient’s unique response to botulinum toxin. Typically, we say a re-injection interval should be about 12 weeks.

Botulinum toxin and oral medications are just one part of the overall treatment plan for spasticity. The mainstay of treatment is therapy that consists of stretching, movement, and specially designed techniques to enhance the development of coordinated and functional skills. A well thought out therapeutic plan is essential and should be in place before botulinum toxin is given. Elements of a well designed therapy plan would include appropriate splints to maintain a stretch across joints, “homework” provided by the therapist that fits in with the family’s schedule, a variety of exercises to keep up interest, and clear goal setting.

Demonstrating that a functional benefit comes from relaxing spasticity with botulinum toxin has been difficult to demonstrate scientifically. This may be because it is hard to form treatment groups in which half of the patients receive placebo and not botulinum toxin and because it is really hard to enroll a large enough group of subjects where each person has the same type and severity of spasticity. Nevertheless, when individuals and not groups are studied, beneficial results from botulinum toxin injections are usually reported.
Table 3: Comparison of localization techniques for botulinum toxin injections

<table>
<thead>
<tr>
<th>Method</th>
<th>Time</th>
<th>Discomfort</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspection</td>
<td>&lt;1 min</td>
<td>Needle stick</td>
<td>Better, but nonspecific</td>
</tr>
<tr>
<td>EMG signal amplification</td>
<td>&lt;1 min</td>
<td>Needle stick plus shock</td>
<td>Best, specific</td>
</tr>
<tr>
<td>Electrical stimulation</td>
<td>1-5 min</td>
<td>Needle stick plus shock</td>
<td>Best, specific</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>&gt;5 min</td>
<td>Gel + pressure</td>
<td>Not clear, specific but requires training</td>
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One of the most convincing articles that demonstrates the practical usefulness of botulinum toxin appeared in the New England Journal of Medicine (Brashear et al. NEJM 347: 395-400, 2002). This study used a patient-centered outcome measure to determine the effects of botulinum toxin injections on spastic wrist muscles. The researchers asked the patients to identify what they wanted the botulinum toxin to do before they got the injection. They were given a list of three or four possible choices. After the injection, the patient was asked whether it did what they thought it would do. This study satisfied the most stringent criteria for a reliable research study. It was a double blind, placebo controlled, randomized trial. The researchers were able to demonstrate that the group that got the botulinum toxin did achieve the functional goals that they wanted from the botulinum toxin statistically more often than the patients who got placebo.

Identifying the best place to inject the botulinum toxin is an important issue. There are hundreds of thousands of nerve endings in the muscles. A variety of techniques can be used to identify the optimal area in the target muscle in which to administer botulinum toxin. The most common technique is simple inspection of the muscle for bulk and tautness using knowledge of human anatomy. The use of an EMG (electromyographic) signal which produces a characteristic sound to identify an area in the muscle where there are nerve endings is sometimes also used to improve the accuracy of treatments. For small muscles, electrical stimulation may be used. In this technique, a small electrical shock is applied to determine if the intended target muscle moves. The most recent addition to techniques for identifying the right muscle and right site for treatment is ultrasound imaging that gives a picture of the muscle.

This chart compares the various characteristics of localization techniques. Inspection is quick, painless and the accuracy is fair. EMG signal amplification takes less than a minute to perform. It is more accurate than inspection, but not as specific as other techniques. Electrical stimulation might take longer, but it is probably the most specific technique. Ultrasound takes longer time and it is specific, but it requires technical skill and experience to be able to correctly interpret the images.

Unfortunately, botulinum toxin injections do hurt. A useful approach to minimize discomfort is considerate anticipatory guidance. This consists of telling the patient what’s going to happen by describing the technique in a step-by-step fashion and then using distraction during the procedure. Local numbing cream (e.g., EMLA) or spray (e.g., ethyl chloride) is often used to reduce the pain of the injections and as a distractor. In some cases, a stronger analgesic or sedative is used. My bias is that the risk of side effects from these drugs outweighs the benefits and I prefer not to use them.

Fortunately, treatment with botulinum toxin has a very low incidence of side effects. These are mostly related to the injection itself, like local bruising, tenderness, and swelling. One of the adverse effects that is pertinent to transverse myelitis, is local weakness which may affect surrounding muscles. Some patients who have had adductor muscle injections complain that they temporarily have new or worse urinary incontinence. Problems walking after botulinum toxin treatment have been reported following injections to leg muscles during the period of adjustment that occurs after treatment. This problem is correctable with therapy. It is important to discuss this possibility with your therapist, before you get the botulinum toxin. In addition, it is essential to go over all side effects with the physician before the treatment and to sign a consent form.

I will conclude this article with a discussion about oral drugs to treat spasticity. In general, I have been disappointed with the effectiveness of medications. That being said, there are some oral medications that should be tried, because they can have a potential benefit and can be used to decrease the “background” intensity of spasticity. They can also be used in conjunction with botulinum toxin when additional relaxation of specific target muscles is desired and a specific therapy plan is in place. Unfortunately, oral drugs do have side effects since they are absorbed into the blood stream and circulate throughout the body. They are chemicals that bind receptors in the central nervous system and have the potential to depress multiple higher cortical functions, such as alertness, memory, and concentration.

Most of these drugs alter the function of neurotransmitters or neuromodulators in the central nervous system by suppressing excitation through blocking a chemical messenger called glutamate, or they enhance inhibition of excitation by activating another chemical messenger like glycine. A third mechanism of action is directly on the membranes of the muscles re-

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The Transverse Myelitis Association
sulting in weakness.

Side effects from oral medications to treat spastic muscle tone can be insidious and under recognized. These include alterations in thinking, alertness, mood, and personality. It is prudent to start at a low dose and then gradually increase the dose looking both for effectiveness and side effects.

Despite these drawbacks, oral medications may be successful and should be considered as part of the general medical approach to managing spasticity.

Passive function requires sufficient flexibility and looseness of limbs for caregivers to perform activities that patients cannot perform by themselves. Active function, on the other hand, is what the patient can do alone. Active function requires active range of motion, strength, attention, alertness and a good mood. Thus, the problem with using oral medications is that while it may be possible to enhance both comfort and passive function it may be more challenging to provide a medication that will improve comfort and active function. Unfortunately this is often the goal; you want to feel more comfortable, but you also want to be more active.

Whenever there is a long list of medications to treat a condition, it indicates that there is no one best medication, and that the search is ongoing for the ideal drug. Often times, there is an initial enthusiasm for a new drug and then it is determined that the drug doesn’t work as well as initially believed.

In conclusion, interventions for spasticity can be divided into treatments that affect the entire body or just specific target muscles and into treatments that are either permanent or reversible. Surgeries, oral medications, and injections are “add ons” to the therapy program. They are not a substitute for the therapy itself. There is good evidence that suggests that appropriate therapeutic exercises in combination with preventative measures, such as stretching with well made splints, can result in increased function. We are learning that the central nervous system is a great deal more changeable than we had previously thought. The challenge is to find the right combination of interventions that will help to make those changes happen.

Demyelinating Disorders: Update on Transverse Myelitis
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This article is an update on Transverse Myelitis (TM) based on our experience at the Johns Hopkins Transverse Myelitis Center (JHTMC). TM is a monophasic monofocal demyelinating disorder of the central nervous system and can be classified as idiopathic or disease associated. We diagnose disease-associated TM when there is direct evidence of illness, such as lupus, sarcoidosis or infection, such as herpes myelitis, varicella zoster myelitis. Idiopathic TM, on the other hand, is when there is no known underlying cause of the acute myelitis onset. Of the 356 cases reported in the 36 months prior to publication of the paper, 64% were idiopathic. TM can be a presenting feature of MS in patients who have an abnormal brain MRI at acute onset or other features, such as oligoclonal bands in the cerebrospinal fluid.

Though largely monophasic in 75-90% of patients, several factors can increase the chances of a TM reoccurrence. Having multiple lesions in the spinal cord or in the brain, a mixed connective tissue disorder, oligoclonal bands and serum auto-antibodies in the cerebrospinal fluid can all be factors that put the patient at risk for another attack or conversion to MS.

Most patients with TM experience spontaneous recovery within 6 months and recovery may continue for up to 2 years after symptom onset. It has been reported in the literature that 1/3rd of the patients with TM have good outcomes and 1/3rd worse outcomes. In the patient cohort followed at JHTMC, there is likely a referral bias for severe cases with only 20% of patients who had a good outcome. Recent studies at the JHTMC suggest that abnormally high levels of cytokines, especially IL-6, may suggest poor prognosis and recurrence.

TM affects all ages with bimodal peaks at 10-19 and 30-39 years, and there is no gender or familial predisposition. Clinical characteristics at onset include weakness that occasionally progresses to the upper extremities followed by spasticity. Pain, paresthesias, urinary urgency, bowel or bladder sexual dysfunction are other features of TM at acute onset. Dr. Kaplin and his colleagues have found a high prevalence of depression in patients with TM. However, it is shown that the severity of disability does not correlate with depression. It is currently hypothesized that cytokines, or immune messengers, in the brain play a role in depressed mood. In our case series, depression resulting in suicide is the leading cause of mortality in TM, accounting for 60% of the deaths that we have seen in our clinic (Kaplin, Unpublished observations).

Regardless of the correlation, it is very important to detect and treat depression.

Histopathologic studies of spinal cord tissue obtained from biopsies and au-