

Thank you for allowing me to speak today. We'll be talking on the management of spastic hypertonia: current concepts. My name is Michael Munin, I'm an Associate Professor in the Department of Physical Medicine and Rehabilitation here at the University of Pittsburgh Medical Center.

I'd like to begin the talk by just briefly defining the word spasticity, although as you'll see the word takes on different clinical meanings, but a working definition perhaps since 1980 has been spasticity is a motor disorder characterized by a velocity dependent increase in a tonic stretch reflexes with exaggerated tendon jerks, and this results in hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome. That's kind of a, a mouthful there but essentially I think the last sentence actually has the most clinical relevance, is that it's just one component of this so-called upper motor neuron syndrome. And essentially this is a dysregulation of descending motor control from a variety of diagnoses which we'll highlight in a moment. But from a clinical perspective and we're trying to keep the talk today as clinically relevant as possible it, it being spasticity, results in what has been termed positive and negative symptoms.

Positive symptoms would be essentially muscle hypertonicity, spasticity being the hallmark. Again we talked about the velocity dependent exaggerated tendon jerks, but you can also see clonus, flexor extensor spasm, hyperreflexia, dystonia and rigidity. But concurrently we also negative symptoms, and these are primarily weakness from the primary neurological insult. And this results in decreased dexterity, weakness, paralysis, fatigue ability and slowness of movement. So when we talk about

treatments as the talk progresses we are pretty much going to be highlighting the column here I'm highlighting here in positive symptoms. Negative symptoms, the weakness and such can be addressed perhaps with therapy, some bracing methods, but we'll be focusing most of our talk today on the positive symptoms from upper motor neuron syndrome.

So what are common etiologies that we see that cause spasticity? Probably the most common diagnosis would be stroke followed by brain injury, multiple sclerosis, spinal cord injury, cerebral palsy and then we see others such as anoxia and there's a whole host of conditions that fall under the neurodegenerative disease category.

When we assess a patient with spasticity it's important to come up with treatment goals because not all spasticity requires treatment. In fact just because you see some spasticity on examination is, that is not a reason to develop a treatment plan. So it is really important and incumbent on the provider and in communication with the patient and/or caregivers to come up with a treatment goal that is shared by all. These could be in the category on my left here that I'm highlighting, goals that want to be improved, such improvement in range of motion, improvement in walking, improvement in orthotic fitting, improvement in transfers, getting from one surface or level to another, improvement in seating and ease of hygiene, for example in the perineal after bowel/bladder function. Things that could be decreased with spasticity treatment includes decreased energy expenditure such as in a spastic gait, that could be fatiguing, this could be perhaps improved; decreasing spasm frequency; decreasing pain and for those who are quite disabled, decreasing caregiver burden.

This is a nice little chart from Mitchell Brin from 1997 that we're just adapting here. This is a nice summary of how perhaps to conceptualize when and how to treat patients with spasticity. So we assume that coming in patients present with spasticity as a problem, and then we evaluate is that problem something that requires further treatment? If it's no, then no treatment is indicated. If we see spasticity and it indeed causes a problem the next step is to identify functional objectives if they exist, patient and caregiver objectives and technical objectives, what's technically feasible? And then once all these three aspects are analyzed we then initiate a comprehensive management program.

So at this point I want to change gears a bit and we'll just talk about some common clinical phenotypes, essentially these are common presentations we see in our office, perhaps you see it in yours when treating patients with spasticity and I want to highlight just some of the muscles and joints that are involved so that when we talk about treatment we get a sense as to who and what we are treating.

So upper limb spasticity patterns, they can occur when muscles for example over here that teres major latissimus being here are spastic, pulling the shoulder downward into extension and to the chest wall in adduction. The adduction is often caused by the muscle highlighted here in the pectoralis major, and you see the large palpable band of the muscle here.

Other common upper limb spasticity patterns, elbow flexion, these are caused by the biceps, the muscle beneath it and the brachialis typically assessed in the distal lateral aspect but shown here on the medial side. And of course the brachioradialis which crosses the elbow joint sub-served by a different peripheral nerve but these are key muscles that flex and cause a spastic elbow posture.

In the wrist the common muscles would be the flexor carpi radialis identified here, ulnar to that would be the flexor carpi ulnaris, this patient doesn't have one, but in between could be the palmaris longus and you can see that tendon could be palpable if it existed, which this patient does not.

In the hand we have thumb and palm deformity shown here, the flexors are caused by the flexor digitorum superficialis which is the ipsilateral joint flexor, the flexor digitorum profundus, which is the distal flexor which has joint innervation by both the median and ulnar nerves, in the thumb you have the distal IP flexor, the flexor pollicis longus muscle shown up here but it attaches there. Then you have the flexor pollicis brevis, which is the short flexor which flexes more at the CMC joint and the abductor pollicis between the second metacarpal and the thumb brings the thumb inward into adduction. All of these muscles contribute to the posture shown.

Another thing that perhaps is not as well appreciated is the spastic hand that can cause swan necking and boutonniere type deformities. Now if I just showed you this and asked what the diagnosis was often I, I get an answer which would be not surprising that this is a rheumatoid hand, someone with rheumatoid arthritis. But indeed this picture here is a patient with a spastic hand and it occurs due to

spastic overpull of in this case some of the wrist extrinsic extensors, some of the flexors, some of the lumbricals and you get this very characteristic swan necking and other deformities but this is due to spasticity.

Here we see a typical hand where there is spasticity of the lumbricals, remember the lumbricals originate off the flexor tendons in the mid-palm, insert onto the extensor hood mechanism and they flex the IP, excuse me they flex the MCP joint and extend the IP and DIP joints given this characteristic hand that has 90 degree flexion at the MCP joint.

Here are some common lower limb spasticity patterns. Well, we can see very characteristic equinovarus deformities at the foot, multiple muscles contribute here, we are showing this diagram, the gastrocnemius, gastroc and \_\_\_\_\_ at the soleus, although really the gastrocnemius is the much more important muscle, the soleus is more of a static muscle, not quite involved in spastic equinovarus posturing. The flexor digitorum longus is a very important muscle on the medial side of the tibia, tibialis posterior also important. Along the anterior compartment believe it or not the tibialis anterior and you can see the tendon attachment from the tibialis anterior where my mouse cursor is here, that's an important supinator of the foot, very prominent in the spastic equinovarus foot. You have flexor digitorum brevis, which is the short toe flexor, bending the first IP joint, and at times you'll even have involvement of the extensor hallucis longus. So all of these muscle contribute to the spastic equinovarus foot. Here we are showing, here's another close up picture, you can look at the

toe flexion here and we are also showing once again the tibialis anterior and I don't know how well it comes out on the picture here, but you can actually see the tendon hypertrophied here.

In the proximal hip muscles the adductor muscles are important for thigh adduction, it looks like Dr. Alberto Esquenozi is the physician here, modeling here, one of our colleagues from the eastern part of the state. He is showing us that there are adductor muscles, the adductor brevis, the adductor longus attaching here at the pubic tubercle, porcellus and of course more inferior the adductor magnus muscle. These muscles bring the thigh inward and would be important contributors to a narrow based spastic gait or to issues with perineal care. Lastly we have the muscles that cross the hip and knee joint that cause the so-called stiff legged gait syndrome, rectus thenaris being the primary one outlined where the mouse marker is moving and more lateral to that the vastus lateralis both innervated by the femoral nerve.

So we'll just digress very quickly to the pathophysiology of spastic hypertonia. Again, you see a patient here with a flexed elbow, almost what I call a boxer position, the, the fist is clenched, sometimes even out in front, and here you see equinovarus posturing at the foot.

Typically three mechanisms or three etiologies in terms of why spasticity develops have been considered: lack of control, which is a loss of descending inhibition, interruption of Renshell firing, there has been motor neuron excitability postulated due to denervation hypersensitivity where the remaining motor neurons are hypersensitive to the neurotransmitters that they see. And others have

talked about collateral sprouting. Newer ideas have come about and there have been recent studies looking at the genomic issues and gene regulation in spasticity which I think are important areas in research. Hopefully we'll learn a little bit more about what causes this common presentation as this research matures.

Another thing we have to also consider are the musculoskeletal effects of spasticity, namely along the joint and tendon. So there is a progressive chain of events, spasticity can lead to disuse and immobility, this can then cause contracture, shortening of the perimysium, the connector tissue around the bundles of sarcomeres, this causes further contracture and then a loss of sarcomeres which are the active component of muscle contraction and then finally over time muscle is replaced via connective tissue and you get more permanent contracture and erosion of motor and muscle tone.

This is a nice overall summary by Gracies, initially published in Muscle and Nerve in 2005 which we have modified just ever so slightly. So essentially if you want to see the interrelationship between the various reasons why spasticity occurs, it always has to begin with damage to the central motor pathways or CNS. Acutely you develop – the patient would develop paresis. From paresis you have immobilization and shortened positioned, shortened positions, and of course disuse if severe. This causes as we talked about soft tissue muscle rearrangements and then contracture as we just highlighted. On the delayed side, on this side where my mouse is being – showing you on the picture here, there are CNS plastic rearrangements that occur at the supraspinal and spinal level, again we highlighted briefly some of the mechanisms postulated. Regardless of why it occurs, the end result of

these plastic rearrangements lack of descending inhibition is muscle overactivity, giving you three basic phenotypes, spasticity, spastic dystonia and spastic cocontraction, and most people will talk about these interchangeably. We'll talk briefly about various differences between these presentations, but essentially they are all under the muscle overactivity heading.

So spastic dystonia is more seen when there is tonic muscle contraction of both flexors and extensors, but this is typically in the absence of phasic structure voluntary effort, the patient here in the middle is showing a cervical dystonia. Here we see a dystonic posture of the foot, and this is a writer's cramp or a task specific dystonia in the hand here.

Spastic dystonia can lead to cocontraction, essentially contraction of agonist and antagonist. So this is an example where the ankle is being moved, here the ankle is being moved down and you see the graph here, and then in terms of down being plantar flexion, and then it's being moved up in this area that I'm highlighting, this would be dorsiflexion. The first EMG trace, this is just a surface EMG trace over the gastrocnemius muscle, excuse me over the tibialis anterior muscle, the second or bottom trace is over the gastrocnemius muscle. So you see when the patient is asked to plantar flex the foot, that's the down, down, down indicated by the curve here, as one would expect the gastrocnemius fires aggressively as it should, and as it should the tibialis anterior is fairly quiet. Remembering when the agonist fires, in this case the gastrocnemius, the antagonist should not fire. However when the patient attempts to do – to raise the toe, i.e. dorsiflex the foot, as one might expect, the tibialis anterior, the dorsiflexion muscle is showing a good burst of EMG activity but what



we are also seeing that is pathological is the gastrocnemius is firing down here. This should not occur, this is a definition of spastic cocontraction whereas agonist and antagonist muscle fire concurrently.

Okay, we're going to again shift gears here and we are giving kind of a quick review of a lot of different topics so we're going to keep moving here. And now we are going to talk about therapy treatment options. If you look at the literature there are a lot of things that are being evaluated, cold or ice, biofeedback, acupuncture, therapeutic ultrasound, vibration recently and electrical stimulation be it FES, \_\_\_\_\_ muscular electric stim. In most of these studies efficacy is not well documented, there are the occasional positive studies. For example in acupuncture there is about 3 or 4 trials I'm aware of, I think 3 of the 4 show no difference, 1 shows a modest difference. These are all small trials. For the most part taking cold and vibration as examples, benefits are documented when the modality is applied, but they are transient and when the modality is removed spasticity recurs.

Splinting has been evaluated. It is typically ordered on a routine basis in patients with spasticity, these could be upper or lower limb splints or a fauces. These could be passive or dynamic, meaning there is some tension to the splint. The important thing in the upper limb is that we see often a mistake in that patients are braced in the typical, I would call this a C position where the wrist is in a certain amount of wrist extension, the fingers and thumb are flexed in what I call a C, which is a balanced orthosis, termed a balanced orthosis, a typical orthosis for someone with an orthopedic tendon injury for example. But in spastic disorders where there often is a flexor overpull greater than extensor, and

patients fingers are postured in a flexed manner, this type of splinting actually shortens muscles in a way we don't want. So we, we recommend or advocate spasticity splints for essentially splints where the thumb is in abduction, the fingers are more in extension. These however are not functional splints, and are worn statically typically at night.

It's important to note that the problem with splints, why they make a lot of sense to, to stretch out spastic muscles and tendons to try to avoid the Sarcomere shortening and loss of Sarcomere as we mentioned before, it is often very, very difficult to get patients in these orthoses when their hands are so spastic and tight that you can have skin breakdown, it is painful and often they are abandoned. But there has been some analysis to suggest how effective this approach is. I refer to a recent study by Katalinic, this is just this year in the journal – therapy journal, Physical Therapy. This was an electronic database search conducted through June of 2010, they looked at all randomized control trials and control of clinical trials of stretch, and this was applied for the purposes of treating or preventing contractures in neurological conditions of which spasticity was often a large part of this. They found 25 studies that met their inclusion criteria.

They saw moderate quality evidence that stretch has a small immediate effect on joint mobility in this neurologic population. However, and this is unfortunately the take home message from the study that high quality evidence showed that unfortunately there was little or no short or especially long term effects on joint mobility, pain, spasticity relevant to this talk or activity limitation in people with neurological conditions who were treated with splinting.

So you know should you use this? You know probably early on it makes some difference just to prevent an early problem, but again for a long term benefit we probably don't advise – and there are some perhaps some exceptions, I get to one right now. In children with cerebral palsy, a study by Kanellopoulos in 2009 in the European Journal of Physical Medicine and Rehabilitation showed that splinting, and this is important, combined with botulinum toxin injections did show a modest positive effect in upper limb function in children with cerebral palsy. So that perhaps in combination splinting does offer more benefit, and I'll get to the combination effect, because you'll hear that term as we move forward, but as far as a single modality splinting in spasticity not so effective.

Well let's move now onto the pharmacological treatments. So there are a variety of medications that have been used, the Benzodiazepines Baclofen, Dantrolene Sodium, Tizanidine, Clonidine, Gabapentin, 4, you know Peridium which is a new one that's just come out, there's a lot of other things, there's some new medications under development. I won't get into the individual pharmacology of each but I do want to summarize the benefits and drawbacks of oral medications as a generalized class. A, they are easy to administer, they are most helpful when there is global spasticity defined as spasticity affecting more than 2 regions of the body, for example if it's just an arm and a leg, that would be more of a regional approach; but let's say it's hemiplegia including the trunk, head and neck, that's global and, and oral medications are a very efficacious and logical way to start. They do decrease hyperreflexia, they seem to reduce painful spasms.

Side effects: they can cause sedation as doses are escalated, and these could be such problematic that patients, even though they are getting some benefit, beneficial effects with spasticity reduction don't want to take the medication. Certainly they can cause weakness as the dose is escalated, they can cause confusion, nausea, dizziness, orthostasis, they can also lower seizure threshold. And one of them, Dantrolene, at higher dose perhaps more than 4 milligrams per day also has the potential of hepatotoxicity and even death. And so in those cases, liver function studies need to be followed, as is with Tizanidine, although not nearly as severe in terms of the hepatotoxicity effect, potential effect. But the medications are a very useful part of our treatment and we do use them often.

I think what is probably more efficacious when there are perhaps the focal goals for treatment is chemo-denervation, and in our center we, we are pretty much on the forefront of this and we, we do show nice outcomes in treatment with this. And so I want to highlight some of what we do and at least illustrate some of the pros and cons here.

So chemo-denervation is – can be loosely defined as local muscle or in fact nerve relaxation to diminish spasticity by a more distal mechanism, i.e. downstream at the nerve muscle neuromuscular level as opposed to oral medications are typically at the brain, brain receptor or intraspinal receptors. This of course in an injectable therapy, it is temporary, reversible and titratable. We are talking here about the Botulinum toxins, but there are also neurolytics that block nerves, they would include Phenol and Ethyl Alcohol.

I'll first talk with Alcohol/Phenol, and I'll lump them together so if I say Phenol, I'm – just for the ease of presentation it's Alcohol and/or Phenol. If – these have been around for example for I don't know, 40, 50 years and they have a long, long history of use. When they are placed around nerves they denature protein, they cause tissue necrosis, it destroys the outer layer of the nerve affecting all the axons, but really it affects the axons closest to where the fluid is, and I'll show you some real specific examples of this. So now – so typically the entire nerve is not neurolysed and because you can get afferent fibers as well as those are the sensory fibers as well as the efferent motor fibers you often can get reductions in spasticity without significant paralysis. It is low cost, which is very nice. And there is no antigenicity if used over time.

So how does it work? The duration of effect is related to the area of denervated segments to the dose, so in this little cartoon I'm showing you the lightning bolt is the needle electrode, the circle is the area where the fluid has touched the nerve, the nerve is that long oblong structure here, and what happens is over time there is regeneration and regrowth of axons occurs, but you can get some fibrosis and this occurs typically with repeated injections.

What are some of the literature showing with Alcohol or Phenol injections? Well, really quite nice duration, 6 to 12 months, 2 or 3 years in limited patients in this older study by Tardieu, Phenol whether it's the tibial nerve or other nerves that were injected again 10, 22, 36 months. I typically tell patients 4 to 6 months using low dose targeted injections that we do in our practice.

So what are the common nerves that we use Phenol with? And we are using a 6% Phenol, you have to use either a 5 or 6% concentration to get the neurolytic effect, lower concentrations only give an anesthetic effect with that neurolysis. So these are perhaps the 6 main things that we do routinely in our practice, we will block the obturator nerve for the adductor spasticity pattern, musculocutaneous nerves for elbow flexor pattern, the motor point to rectus femoris to diminish stiff legged gait, motor points to the hamstrings where there is excessive knee flexion, motor points to the tibial nerves when there is an Aquinas foot deformity, and at times femoral nerve, especially those perhaps in multiple sclerosis where sensation is greatly impaired but that muscle is, or that nerve is really causing a lot of problems but we don't have to worry about sensory effects.

So what I'm showing you here is actually a live ultrasound of a musculocutaneous nerve block. What you see is the twitching of the nerve stimulator, this is the needle here, the arrowhead is the musculocutaneous nerve and there is the fluid from the nerve block around this portion, you see that blush you just saw, that's the injection coming in. Notice here that on the posterior aspect of the nerve we're really not getting much fluid, so really we are blocking only those axons in this part of the nerve. But that block was about a cc, so using musculoskeletal ultrasound we are able to directly see the needle get to the nerve, avoiding blood vessels, we are using very low volume and that helps to prevent side effects. And side effects can be severe if technique is sloppy, which could be dysesthesias, tissue necrosis, so that the use of ultrasound is a novel advance in the use of Phenol nerve blocks.

So let's talk about the other injectable therapy that we use often, and that is the Botulinum toxin therapy. Botulinum toxin is a purified toxin from clostridia bacteria. There are many side – many serotypes based on the target receptor of the specific toxin. In the United States there are now four approved toxin medications for the treatment of cervical dystonia. I've listed their trade name and then their generic name, all of them have the suffix Botulinum toxin A, or for the one Botulinum toxin B, but the prefix is different, there is Ona, Abo, Inco and Rima. So for example, Dysport is Abo Botulinum toxin A, Myobloc is Rima Botulinum toxin B, Botox-Ona Botulinum toxin A, and Xeomin is Inco Botulinum toxin A. For upper limb post-stroke spasticity one medication, Ona Botulinum toxin A has been approved.

The Botulinum toxins will include Tetanus, because that fits with this, although of course not used medically, has receptors primarily either the cellular signaling receptor on the molecular that is attached to each vesicle acetylcholine, that would be the synaptobrevin or the pre-junctional protein complex that causes the vesicles of acetylcholine to bind to the pre-synaptic membrane after which time the acetylcholine molecules are released into the synaptic \_\_\_\_\_, that's called the SNAP 25 complex, so if synaptobrevin or the SNAP 25 is cleaved by one of these toxins the vesicles cannot bind, neurotransmitter is not released, and chemo-denervation then occurs.

So just – we talked – we understood what we were talking about, this is a histological teased out specimen, this is a distal terminal nerve, these are terminal nerve branches, this little football shape here is the neuromuscular junction here, or the end plate. And so when we inject into the muscle these

are all intramuscular, they have to be intramuscular injections, in fact if you inject into the subcutaneous tissue you are wasting the medication. So the muscle is injected intramuscularly, the endocytosis is taken back up through into the end plate here, the terminal nerve. There is some retrograde transport but it is through this mechanism that these medications work.

So here is an example of Botulinum toxin we are injecting here at the pronator teres, again this is the needle here, this is the pronator teres, these muscle here. This is the flexor carpi radialis, again you see the blush, you see the fluid enveloped, the pronator teres, again ultrasound is a very nice modality to make sure that special and multiple muscles overlap like we are seeing here in the forearm, we can keep our toxin preparation just in the target muscles. So you are seeing again just the pronator teres being injected in this ultrasound demonstration.

So is botulinum toxin long lasting? Well, it lasts for about 3 to 4 months then, and this is botulinum toxin A but the same thing is for B as well. There is reestablishment of new neuromuscular junctions and plate terminals. So this is perhaps – let me go back here – this is the end plate that we have blocked and chemo-denervated roughly 2 to 4 months later from the terminal nerve a new sprout is developed and a new, new muscular junction is formed and by about 4 to 5 months for most patients, the effects of the injections totally wear off. So if there is good therapeutic benefit and patients like the outcome, these injections do need to be repeated. For spasticity I would say 3 times a year, for certain patients with cervical dystonia, spasmodic torticollis, who are more sensitive, have more pain, perhaps 4 times a year.



So some of the overall effects of the botulinum toxins, these are injected into overactive muscles, this is a focal temporary chemo-denervation. The onset is typically 24 to typically 72 hours, it can take up to 2 weeks, which is not uncommon. The maximum effect is approximately 4 to 6 weeks, again the clinical benefit is between 12 to maybe 16 weeks, and it can be used with other therapies, and this is an important point because I believe that for maximal effectiveness and we'll show you a study that we performed later in the talk, the combination effect, we talked about the earlier study with splinting and the botulinum toxin therapy. I think that the use of multiple modalities is critical to maximize our treatment goals in patients with spasticity.

I guess before I get into combination we should talk about some of the, the negatives of toxin therapy, the main one being its cost. I told you that phenol is dirt cheap, the botulinum toxins are not. And so cost is, is an issue. There is also a maximum dose that you can use, if you go higher than that there are other risks that include remote spread of the toxin with diffuse weakness in remote muscles that can cause problems such as dysphagia affecting the swallowing muscles even when the arms and legs are injected. And so and over time could be immunogenicity, and I think we'll talk more about the immunogenicity effects later here.

But getting back now I'm going to switch back to combination treatment effects, or combination treatment. So I showed you phenol with neurolysis, I showed you the botulinum toxins with chemo-denervation, why not combine the two? And we find we do this quite often and we find it very, very

helpful. By doing the phenol nerve blocks we are able to inject single nerves that sub-serve large proximal, powerful muscles, we get a very good clinical effect. And this spares toxin dosing, lowers the amount of toxin we need to inject in the other muscles that are harder to get technically where toxin has an advantage, but because we are using less total dose it's more cost effective and certainly less chance of side effects.

The botulinum toxin, abbreviated BTX, is best for the small distal muscles and it's best for selective targeting. I should mention that even with ultrasound phenol is precise, you are really hitting a needle in the haystack. I think using a nerve stimulator and ultrasound makes the job so much easier, but even under skilled hands it's difficult, whereas botulinum toxin is easier to hit muscle, the hard part with botulinum toxin is to get the key muscle. I think that's where ultrasound plays a role and in fact we have a recent paper out looking at ultrasound versus just surface anatomic landmarks and we showed in that one paper an upper limb spasticity that ultrasound was more accurate. So that's more on the technical side of how to do the injection, I guess I'm talking just here about why you'd want to combine and how it could be potentially more effective.

So what if these expensive botulinum toxin medications are injected and we are not getting the response we want? Well what are some of the common reasons that we see? First, and this is the most common thing, reason that I see in my practice is that muscles injected perhaps are not the primary drivers of spastic posture. We talked about earlier in the talk in spastic cocontraction I showed you how the gastroc muscles were not letting go when the patient was trying to dorsiflex.

Well what if you mistakenly injected the dorsiflexors because you misunderstood what was driving the spasticity pattern. That can make the natural spastic dystonent posture worse. So you have to understand the pathokinesiology and pick the right muscles or nerves to get the desired effect. Localization not accurate, we talked a lot about the use of ultrasound as a recent modality to make that less and less a concern. So important when again these medicines have to be injected into muscle, not into subcutaneous tissue, and have to go deep to where you want to go you can block a deeper muscle but not the muscle of interest and not giving you the desired effect. Other issues, dose may be a bit too low. And over time we often see a change in the pattern of muscle involvement, so initially perhaps certain muscles are driving the spasticity pattern, but as that's treated, not as much of a concern, but maybe other muscles that were not treated become more, more to the fore and have to be reassessed and added to future regimens.

Lastly, there could be inappropriate reconstitution or storage. Many but not all the toxin products have to be refrigerated. Some have to be reconstituted from a crystalline state and used immediately, others can be stored to a bit later. If you don't follow the rules you can lose potency with the – with the drug that you are injecting. And then for the botulinum toxins, although not with phenol, you can get neutralizing antibodies. Some controversy as to how much of a problem that is, but I still think we see it in a few patients, not that many. But most of us don't want to run into that problem because if the neutralizing antibodies were to develop it could take away this form of treatment for patients in that they would potentially not respond to any injectable botulinum toxin medication.

Getting back to the concept of combination therapy I want to highlight a paper that we did, Doug Weber of our group was the lead author here in the 2010 study in the Archives of Physical Medicine and Rehabilitation. This was a 23 subject study where we wanted to see in combination what, what assets of combination are helpful. So we took common things that are prescribed. And one group got botulinum toxin, and again this was for upper limb post-stroke spasticity. Botulinum toxin, repetitive task practice therapy, another group got botulinum toxin and repetitive task practice therapy in a protocolized method, and then got FEX, Functional Electro-Stimulation in a device that they would wear on their forearm that would stimulate the wrist extensors to help them grasp and release that was used in a training protocol that was pretty rigorously designed.

We had three main outcomes. In Panel A the motor activity log-observation; B is the motor activity log self-report, essentially A and B are the same, one is an observer base, one is the patient subjective base; and the panel C is the ARAT. And A and B have different subscales, 1 to 4, C has up to 50 or so and so that's why the Y axis has different numbers on them. The dashed lines are the groups that got the botulinum toxin and the repetitive task practice, the green lines got those two things plus the addition of electric stimulation. And I should mention who these people were. These were people who were fairly disabled from spasticity, they had a little bit of pinch, a little bit of grasp, that's about it. They couldn't be so paralyzed where they had no functional use, but they had just a little bit of squeeze, very spastic, not the kind of patients that perhaps we are seeing in other upper limb post-stroke trials such as the EXCITE Trial, where perhaps only 3 to 4% of patients had any amount of spasticity in that larger trial. These were all fairly disabled patients.

And so I think one of the take home messages, no matter what regimen we used if you look at the baseline which is the BL to 12 week follow-up they all gained function. And it's also important to note that this data is a functional outcome measure. So we are not just measuring muscle stiffness as the primary outcome, these are all functional measures. And so function improved in all groups by 12 weeks. There was not much of a difference however between the two groups, so it looks like the addition of functional electrical stimulation did not add much more than just having the botulinum toxin and task practice therapy. But these are all significant gains from baseline to 12 weeks, baseline to 12 weeks all were significant at 6 weeks, here 12 weeks not quite as significant from baseline so this is the one that wasn't as significant at 12 weeks. But all were significant at 6 weeks. The trial ended at 12 weeks, so we don't have further data past there. But I think the take home messages here are again combination therapy, the use of botulinum toxins and a specific type of therapy called repetitive task practice can be quite helpful in these patients.

Well, again we are going to kind of move across the spectrum of treatment here in the last 5 to 10 minutes of the talk we're going to talk about some surgical interventions that are often useful. Orthopedically especially for the lower limbs we utilize tendon transfers. The goals of these surgeries, surgical procedures are to weaken overactive muscles. It modifies the primary function of the muscle at the joint in question. So I think the top three are the ones we, we recommend the most: the split tibialis anterior transfer or the SPLATT technique, Achilles tendon lengthening when there is equinovarus deformity, and the FDL, Flexor Digitorum Longus lengthening. And if you can

remember back earlier in the talk when I showed you pictures of some of the spastic equinovarus and supination deformities of the foot I tried to highlight some of these key muscles that were the main movers, so if they don't respond to chemo-denervation therapy, these types of orthopedic surgical procedures are often very, very effective. There are others as well, but I think the top three are what we recommend most often.

The other therapy that's done commonly from a surgical perspective is intrathecal Baclofen. And this is via an implantable pump, Baclofen as you know we talked about it as an oral antispasticity medication, but here we are talking about for global spasticity where it's not just a region or two, a catheter that is inserted into the intrathecal space, it is tunneled to the front of the abdomen in the subcutaneous area, a pump is then placed. This pump is programmable and allows dose titration to give optimal benefit. This is very effective in reducing spasticity. We have found that it is most effective for truncal and lower limb spasticity. There is some effect on the upper limbs but clearly it is not as great as trunk and lower limb, and it is most helpful for spasticity of cerebral and spinal origin.

There are risks, because this is an implantable device that one needs to be aware of. Drug side effects most commonly would be hypotonia, somnolence and this is often if the dose is very high or perhaps there's a catheter malfunction, relative to oral dosing I should mention which is 1,000 times milligrams because it has to have hepatic clearance, these medications are typically 1,000 times less in terms of milligram dosing because they are dripped right into the intrathecal space, into the spinal

cord where there are receptors where the medicine can bind. High doses however can cause nausea or vomiting, headaches and dizziness.

The infection risk we quote is 1%. That's not insubstantial. There can be overdose, or withdrawal if patients forget or are just noncompliant with their scheduled refills. So you need a compliant patient who will not miss the scheduled refill session. We have seen catheter migration and even pump failure, so these need to be watched, assessed and then repaired if problematic.

It's important to note, again keeping with my theme of combination therapy, that ITB therapy can be combined with other treatments such as oral medications and injectable botulinum toxins. Positive outcomes in terms of studies have been documented in spinal cord injury, acquired brain injury and even in stroke. And in stroke it's important to note that the contralateral side often is not weakened even though those intraneural connections are potentially getting the same medication as the affected neurons.

Okay, well at this point I'm going to summarize and close the talk here. We really tried to hit on the whole breadth of current concepts in the management of spastic hypertonia, showed the current treatment options, we talked about rehabilitation, oral medications, chemo-denervation with both phenol and botulinum toxins, we talked about orthopedic surgery and intrathecal Baclofen. I think two take home messages are that one, multi-modal approach based on functional goals is best, and

that not all spasticity requires treatment. This is where goal planning and assessment is really of most importance in order to get best outcomes.

I thank you and appreciate the time that you have, enjoy your day.