National Government Services, Inc.

Moderator:
Olatokunbo Awodele, M.D.
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Coordinator: Thank you for standing by, and welcome to the Multi-Jurisdictional CAC meeting. For the duration of today's conference, all participant lines are on a listen-only mode. Today's conference is being recorded. If you have any objections, you may disconnect. It is my pleasure to turn the call over to your host for today, Dr. Ola Awodele.

Dr. Ola Awodele: Thank you very much, Holly. Good afternoon, everyone, and welcome to the Multi-Jurisdictional Contractor Advisory Committee, or also known as a CAC meeting, on botulinum toxins injections. My name is Ola Awodele, as she said, and I'm a Contractor Medical Director with NGS. This is a multi-jurisdictional CAC, as it says on the title, and that means that it's all of the MACs, Medicare MACs that have parts A and B that have come together to have this CAC meeting.

And everyone will be participating today. And that includes National Government Services, as I said, we're acting as the host, Noridian, Novitas Solutions, First Coast, Wisconsin Physician Services, Palmetto GBA, and CGS. The purpose of today's session is outlined in CMS IOM Publications 100-08, Chapter 13, Section 13.2.4.3, which basically says the purpose of today's meeting is to listen to our distinguished subject-matter experts who

have volunteered to evaluate the medical evidence regarding botulinum toxins for various disease conditions.

Please understand that this meeting is open to the public. However, only the contractor medical directors and the subject-matter experts will be speaking during this call. Each of the seven contractor medical directors, if you could please introduce yourselves, and by that, I mean the people who will be asking the questions by disease category. Thank you.

Dr. Claudia Campos: Hi. Good afternoon, everybody. Thank you for being here, and thanks for the introduction. My name is Dr. Claudia Campos, and I'm with First Coast and Novitas. Thank you.

Dr. Bob Kettler: Hi. This is Dr. Bob Kettler with WPS.

Dr. Meredith Loveless: Hello. This is Dr. Meredith Loveless with CGS.

Dr. Eileen Moynihan: Hi, Eileen Moynihan with Noridian.

Dr. Scott Trimas: Hi, Scott Trimas with Palmetto.

Dr. Ola Awodele: Thank you very much. Before we go any further, I will also ask our panel of experts who are located across the various jurisdictions to please introduce themselves. When you're doing so, please state your name, your affiliation, and acknowledge any possible conflicts of interest. So, if we can begin with Dr. Prakash Gyawali, please. Dr. Gyawali?

Dr. Prakash Gyawali: Yes.

Dr. Ola Awodele: If you could please introduce yourself and state - by stating your name, affiliation, and any possible conflicts of interest. Thank you.

Dr. Prakash Gyawali: This is Prakash Gyawali at Washington University in St. Louis. I'm an esophagologist, and I have no conflicts of interest.

Dr. Ola Awodele: Thank you, sir. Dr. Kelly Andrzejewski.

Dr. Kelly Andrzejewski: Hi. I'm Dr. Kelly Andrzejewski from the University of Buffalo in Buffalo, New York. I'm a movement disorder neurologist in Buffalo, and my only conflict is I'm a speaker for Teva.

Dr. Ola Awodele: Thank you. Dr. Subramanian?

Dr. Prem Subramanian: Hi, this is Prem Subramanian. I am at the University of Colorado, Sue Anschutz-Rodgers Eye Center in Aurora, Colorado, and I am a neuro-ophthalmologist and orbital surgeon. I have no relevant conflicts of interest.

Dr. Ola Awodele: Thank you, sir. Dr. Shiayin Yang?

(Linda): Hi. This is Linda. She will be joining later.

Dr. Ola Awodele: Okay. Thank you, Linda. Dr. Pham Chau?

Dr. Pham Chau: Hi. My name is Chau Pham. I am an oculofacial plastic surgeon here at the University of Iowa. I have no relevant conflicts of interest.

Dr. Ola Awodele: Thank you. Dr. Tesha Monteith?

Dr. Teshamae Monteith: My conflicts of interest include advisory board for AbbVie, also educational grants for (Merz's) advisory work or consultation work, and not quite yet, but soon-to-be clinical trial for Ipsen, and also ongoing clinical trial for AbbVie. I have other conflicts of interest as it relates to other therapeutic products, but not specifically neurotoxins.

Dr. Ola Awodele: Thank you. Could you state your affiliation? I think we only kind of heard half. We only heard the conflicts of interest. We didn't hear you introduce yourself nor your affiliation.

Dr. Teshamae Monteith: Yes, my name was already mentioned. I'm Dr. Teshamae Monteith at the University of Miami Miller School of Medicine. I'm Associate Professor of Clinical Neurology.

Dr. Ola Awodele: Thank you. Thank you very much. Dr. Sonya Knight.

Dr. Sonya Knight: Yes, hi, I'm Dr. Sonya Knight. I am a private practice neurologist and psychiatrist with a practice in outskirts of Philadelphia called Neurology Psychiatry and Balance Therapy Center. And I have no relevant conflict of interest.

Dr. Ola Awodele: Thank you very much. Dr. Park.

Dr. Amy Park: Hi, my name is Dr. Amy Park. I'm a urogynecologist at the Cleveland Clinic. I also am here on behalf of the American College of Obstetrics and Gynecology.

Dr. Ola Awodele: Thank you. Dr. Ferzandi? Thank you. Dr. Ferzandi? Okay. Dr. Garrett?

Dr. Gaelyn Garrett: Hi, I'm Gaelyn Garrett. I'm an otolaryngologist at Vanderbilt University, and I specifically specialize in voice disorders. I have no conflicts of interest.

Dr. Ola Awodele: Thanks. Dr. Baratta?

Dr. John Baratta: Hi, my name is John Baratta. I'm an assistant professor in physical medicine and rehabilitation at the University of North Carolina in Chapel Hill, North Carolina. I have no relevant conflicts of interest.

Dr. Ola Awodele: Thank you. And Dr. Kwasnica.

Dr. Christina Kwasnica: Hi, this is Dr. Tina Kwasnica. I am the Chair of Physical Medicine and Neurorehabilitation at Barrow Neurological Institute, and my conflict of interest is Speakers Bureau for AbbVie.

Dr. Ola Awodele: Thank you very much. So, next on the agenda are key questions and discussions. So, prior to this meeting, our CMDs from all the MACs completed a review of the literature and prepared a list of articles for review by our subject-matter experts. Our panel of experts will comment on these articles and any additional evidence of which they may be aware.

We have prepared a series of questions by disease category, and will ask our subject-matter experts for his or her response and then ask the other subject-matter experts if they have anything to add or discuss. If any of the general questions apply to your topic, please do not hesitate to address this question. This would also be asked by your CMD.

Due to time constraints, please remember we want to limit it to about five minutes per answer. We do understand that there might be more time needed

if necessary. The answers to these questions should be based on the literature and be in alignment with good clinical practice and guidelines.

Also, if the literature is silent or inconclusive on a particular issue, we would appreciate if our subject-matter experts note that. So, we will now begin with the questions, and like I said, we're going to go questions by disease category, and the first one is achalasia, and it would be moderated by Dr. Campos. Dr. Campos? Dr. Campos and Dr. Gyawali.

Dr. Claudia Campos: Did you hear me? Can you hear me?

Dr. Ola Awodele: No, we can hear you now. Yes, we can hear you.

Dr. Claudia Campos: Oh, sorry. Yes.

Dr. Ola Awodele: It's okay.

Dr. Claudia Campos: Is there evidence to support the use of botulinum toxin injections as a treatment for achalasia?

Dr. Prakash Gyawali: The answer is yes. There is evidence, but one has to understand the scenarios in which achalasia can be treated with botulinum toxin, because achalasia is a lifelong disease, and botulinum toxin effects are not permanent. They generally last a median of six to nine months, sometimes a little longer.

And for that reason, patients who have achalasia who can tolerate invasive managements, more permanent managements, tend to be treated better with more durable symptom response with these permanent treatments like myotomy or cutting up the muscle, or pneumatic dilation, which is tearing of the muscle of the lower esophageal sphincter.

So, what the literature supports is using botulinum toxin in a few clinical scenarios. One is in patients who cannot tolerate these invasive treatments because of comorbid conditions. They cannot tolerate surgery, for instance, for myotomy. Or they cannot tolerate an invasive dilation that may have a complication of a perforation that may require surgery, then it is reasonable to use recurrent injections of botulinum toxin.

The second scenario is when a patient has to wait for their definitive treatment for whatever reason. If there is a waiting period involved, then botulinum toxin injections can temporize their treatment. The third scenario is if the diagnosis of an achalasia-like disorder, and this includes other spastic disorders within the broad achalasia spectrum.

If the diagnosis is unclear, before somebody goes and does something permanent that is irreversible, it is reasonable to do a botulinum toxin trial so that if symptoms improve with botulinum toxin in patients where the diagnosis is not completely certain, that will add confidence to doing something irreversible to the patient's esophagus.

And a sub-indication under that category is an achalasia-like pattern that is induced by the use of opioid medication. We have learned about this disorder in recent years, and opioids can create an esophageal movement pattern that can be similar to some forms of achalasia.

And so, sometimes there is a philosophical issue about doing something permanent to the esophagus when it is caused by a medication that could be potentially changed to something else. In those settings, again, botulinum toxin may be a means of temporizing symptoms.

Dr. Ola Awodele: We can't hear you, Dr. Campos.

Dr. Claudia Campos: Sorry. Can you hear me now?

Dr. Ola Awodele: Okay. Yes, we can.

Dr. Claudia Campos: Thank you. Can I follow up with another question regarding the using botulinum toxin to see whether more permanent treatments would be beneficial? Is that still the case with advances in diagnosis of achalasia-like syndromes using functional lumen imaging and complementary physiological testing in addition to high-resolution manometry?

Dr. Prakash Gyawali: Yes. Actually, that has created a bigger need for using botulinum toxin as a diagnostic method because of the higher sensitivity of some of these newer tests in finding obstructive esophageal syndromes. So, the old manometry tests and the liquid barium studies that we were using, do not have the same sensitivity and specificity as some of these newer tests.

And the other issue is, sometimes one test shows an achalasia-like syndrome and the next test may not. The more tests that show the similar pattern increases confidence in how we manage these disorders. So, if there is discrepancy between these tests, or if the newer tests show an obstructive pattern that the older tests that we relied on didn't, then there arises a situation where you'd want to do something temporary to the esophagus rather than something permanent until you're sure that something permanent and irreversible is warranted.

Dr. Claudia Campos: Thank you. And what treatments, if any, should be tried prior to using botulinum toxin injections for achalasia?

Dr. Prakash Gyawali: There are really no other simpler treatments that have a reliable benefit as botulinum toxin does. It is the least invasive of the treatments that provide good relief. For instance, smooth muscle relaxants, medicines like nitrates and calcium channel blockers, have only a 30% to 50% efficacy, with a very high rate of symptoms, side effects.

On the other hand, early response to botulinum toxin is in the 60% to 70%, sometimes even higher, percent range, even though benefits decay in six to nine months. So, among the simpler treatments, the non-invasives, even though botulinum toxin is invasive, and treatments that are not surgery or myotomy of the muscle, botulinum toxin is probably the easiest and the safest.

Dr. Claudia Campos: Great. Thank you. And moving on to some general questions, is there a dose-response relationship with botulinum toxin in achalasia?

Dr. Prakash Gyawali: Okay, so the vast, vast majority of studies have used 20 to 25 units injected in four to five sites in the LES area, so a total of 100 units of botulinum toxin, which is considered the standard dose. When people have tried injecting 200 units, so double the dose, in patients with esophageal spasm, diffuse esophageal spasm, which affects not just the lower esophageal center, but also the esophageal body muscle, results have not been consistent.

So, the standard dose for achalasia and achalasia spectrum disorders is believed to be 100 units in four to five divided doses injected into the region of the lower esophageal center.

Dr. Claudia Campos: Thank you. And is there evidence to support any frequency intervals and total treatment duration?

Dr. Prakash Gyawali: So, again, this goes back to my answer to the first question. It really depends on the individual patient's duration of response and the indication for the injection in the first place. So, if the indication for botulinum toxin is the patient just cannot tolerate anything more invasive, then we keep doing it when the symptoms recur for life.

On the other hand, if it is being done as a therapeutic trial and the patient responds, when the symptoms come back, you would go ahead and do something more invasive. The duration is not fixed, or the interval is not a fixed interval for any given patient, so you wouldn't just schedule a repeat botulinum toxin. You tell the patient to report back when their symptoms recurred, and then plan the next injection, if the plan was for recurring injections.

Dr. Claudia Campos: Excellent. Thank you. And is there evidence to support using botulinum toxin B?

Dr. Prakash Gyawali: There isn't literature to support for or against any other serotypes or any other formulations of botulinum toxin. Now, just based on how botulinum toxin works, if that was what was available, I don't think there would be an issue with response, but there are no specific data that support or refute the use of the B serotype.

Dr. Claudia Campos: Okay. And just our last question. What contraindications exist for the use of botulinum toxin, and what are the long-term effects when you use it?

Dr. Prakash Gyawali: So, there are really no specific contraindications for botulinum toxin other than hypersensitivity or allergy. And in my almost 30 years of doing this, I have not encountered a single patient that was allergic or developed an

anaphylactic reaction to this. Is it possible? Yes. Does it happen frequently? Not really.

So, most of the contraindications and the cautions for using botulinum toxin really are the contraindications and cautions for endoscopy in general, because this is done during sedated endoscopy. And all the risks of endoscopy, including aspiration and the risk of bleeding if the person is on a blood thinner, are real and need to be considered, just as we do for any other endoscopy.

Are there any long-term consequences? The biggest consequence of disrupting or making the lower esophageal center relax is reflux. And indeed, if the patient has reflux, we decide that the botulinum toxin actually worked. If the patient who couldn't eat is now having reflux symptoms, it means that the original problem of the lower esophageal center not relaxing has been resolved, and the reflux that occurs is easily treated with postural measures and with medications.

Now, injection of botulinum toxin can create fibrosis in the sub-mucosal areas, and if subsequent surgery or myotomy were to be planned, it might make the process of dissection a little bit more cumbersome, but there is no evidence to suggest that that risk of fibrosis alone should deter somebody from using botulinum toxin if it were indicated.

There is just one death reported with the use of botulinum toxin that I know of, and that was when the injection technique was probably not followed and some botulinum toxin got into the mediastinum and the patient developed a mediastinal infection and died. But, in general, the long-term consequences mostly relate to reflux, and there are really no serious long-term consequences.

Dr. Claudia Campos: Thank you so much for your

Dr. Ola Awodele: Thank you, Dr. Campos - I'm sorry. Yes. Sorry. Thank you, Dr. Campos, and Dr. Gyawali. I just wanted to remind everybody we have this time - in terms of keeping to time, and I think what I'm going to do is, when you have about five more minutes, (Stephanie) will interject and just call, you know, five minutes more, that kind of thing in time, just so that we can - because we have a packed agenda. So, Dr. Campos, you're going to continue with Dr. Andrzejewski and focal hand dystonia.

Dr. Claudia Campos: Yes. Thank you. Dr. Andrzejewski, are there diagnostic criteria for diagnosing focal hand dystonia?

Dr. Kelly Andrzejewski: I think it's mostly based on clinical exam. Patient complaints of something like writer's cramp, are some of the primary reasons.

Dr. Claudia Campos: Good. And what is the incidence and prevalence of the disorder which would need botulinum toxin treatment?

Dr. Kelly Andrzejewski: If the symptoms are obviously bothersome to the patient, it certainly would be an improved indication to treat them with Botox.

Dr. Claudia Campos: And is there evidence to support the use of botulinum toxin injections as a first-line treatment for severe focal hand dystonia?

Dr. Kelly Andrzejewski: I would say yes, there is. It avoids use of oral medications that can have significant side effects such as muscle relaxants. So, I would say that it should be a first-line treatment, and it's much less invasive.

Dr. Claudia Campos: Okay. And what treatments, if any, should be unsuccessfully used prior to using botulinum toxin injection?

Dr. Kelly Andrzejewski: I don't think there is any. I think Botox should be first-line.

Dr. Claudia Campos: And what objective criteria or scale should be used to measure treatment benefits and outcomes for focal hand dystonia?

Dr. Kelly Andrzejewski: I think you can use probably the dystonia, unified dystonia rating scale and assist with that.

Dr. Claudia Campos: And is that used in clinical practice?

Dr. Kelly Andrzejewski: In some cases, yes. Totally very physician-dependent.

Dr. Claudia Campos: Okay. So, let's move on to our general questions about dosage. Is there a dosage range that you would recommend?

Dr. Kelly Andrzejewski: I think the one supported by the FDA is accurate. That's correct.

Dr. Claudia Campos: Okay. And is there a dose-response relationship?

Dr. Kelly Andrzejewski: Certainly, higher doses can have more significant effects. So, if a patient remains (refractory) to kind of a starting, initially recommended dose, using a higher dose is not - is certainly warranted.

Dr. Claudia Campos: Okay. And is that a trade-off with weakness on one dose?

Dr. Kelly Andrzejewski: Say that again. Is that a...

Dr. Claudia Campos: Is that a trade-off by increasing your dose of botulinum toxin? Would that impair your functionality and causing more weakness?

Dr. Kelly Andrzejewski: Yes, it can cause excessive weakness, but without trial. We have to explain to patients that it's a bit of trial and error. That's why we start low and then if the patient does not have enough response to the first round of injections, the dosage would have to be increased at the next set of injections.

Dr. Claudia Campos: And is there evidence to support any frequency intervals and total treatment durations?

Dr. Kelly Andrzejewski: I think starting typically at every, you know, roughly 12 weeks or three months or 90 days is appropriate, but the importance of having patients as well as physicians or providers monitor, because certain patients do find that botulinum toxin wears off maybe at eight weeks or 10 weeks, and then if that is the case, if that is demonstrated that the patient has benefit, but it wears off earlier, I think there should be indications that it should be able to be approved earlier depending on the patient outcome.

Dr. Claudia Campos: Okay. And is there evidence to support using botulinum toxin B?

Dr. Kelly Andrzejewski: I would say yes.

Dr. Claudia Campos: And are all of them interchangeably effectively?

Dr. Kelly Andrzejewski: Yes, I think they're all interchangeable, but obviously, dosing varies depending on the type of toxin because in most cases, the toxin is not - like one equivalent unit of Botox is not equal necessarily an equivalent to a different brand, one unit of a different brand, with the exception of probably Xeomin and Botox.

Dr. Claudia Campos: Okay. And what is the tolerance development with botulinum toxin and the role of antibody testing?

Dr. Kelly Andrzejewski: I don't typically, in my experience, do routine antibody testing. If the toxin fails to work, then I would switch them to a different brand.

Dr. Claudia Campos: Great. Thank you. And what contraindications exist for the use of botulinum toxin?

Dr. Kelly Andrzejewski: I think other than if the patient is on something like blood thinners that may make - you'd have to advise them that obviously doing injections can put increased risk of compartment syndrome or bleeding within to the muscle compartment. If patients obviously have conditions like myasthenia gravis or other conditions that may already involve neuromuscular weakness, then that would probably be contraindicated.

Dr. Claudia Campos: Okay, thank you. And our last question is, what are the long-term effects of botulinum toxin in dystonia?

Dr. Kelly Andrzejewski: In this case, typically, the effects last on average 12 weeks. Long-term benefit, I think, is improvement in quality of life.

Dr. Claudia Campos: Good. And any downsides?

Dr. Kelly Andrzejewski: No. I think other than the risk of excessive weakness or compartment syndrome, especially in patients that are on anticoagulation.

Dr. Claudia Campos: All right. Thank you so much.

Dr. Kelly Andrzejewski: Thank you.

Dr. Ola Awodele: Thank you, Dr. Campos, and Dr. Andrzejewski, you can stay on because we're going to ...

Dr. Kelly Andrzejewski: I go by Dr. Kelly.

Dr. Ola Awodele: Dr. Kelly. Okay. I also have a name where I tell people ...

Dr. Kelly Andrzejewski: That's what I provide (unintelligible)

((Crosstalk))

Dr. Ola Awodele: ... I tell people just call me Dr. Ola as well, so thank you.

Dr. Kelly Andrzejewski: Yes. Okay, thank you.

Dr. Ola Awodele: We're going to have Dr. Subramanian join you and Dr. Yang, and Dr. Trimas is going to be the moderator. So, Dr. Trimas, take it away.

Dr. Scott Trimas: Yes. Hi. So, thank you for joining us. I have a couple of questions to start with on hemifacial spasm and facial dystonia. So, the first question, is there any evidence that supports the use of botulinum toxin injections as first-line treatment for hemifacial spasms, whether it's idiopathic or secondary to compression?

Dr. Kelly Andrzejewski: Do I go first or?

Dr. Prem Subramanian: Sure. Why don't you go first for this one?

Dr. Kelly Andrzejewski: Okay. So, in my opinion, I think it is first-line treatment. Again, avoid use of muscle relaxants or other medications that can have significantly sedating effects, and it also allows focal treatment versus a treatment that could involve - have side effects on multiple body regions that are taken orally, such as baclofen.

Dr. Prem Subramanian: And I would just add to that there is probably 30 years of literature at least that after a variety of trials showing that 70% to 95%, actually 75% to 95% of individuals with hemifacial spasm, whether it's primary or secondary, will have a clinically relevant response to botulinum toxin injection and that it is very well tolerated in those patients.

Dr. Scott Trimas: Anybody else for that first question?

Dr. Ola Awodele: Dr. Trimas, sorry, I just wanted to interject. We're hearing a lot of typing going on online. Could that person please mute themselves, please? Thank you very much, because it's being recorded, just so that it can be clear on the recording. Appreciate it. Sorry, Scott, you can continue.

Dr. Scott Trimas: That's okay. Is there any other - I have a third person. Is there any other comments on that first question? No? Okay. So, the second question is, what treatments, if any, would be considered failures prior to using botulinum toxins for hemifacial spasms?

Dr. Prem Subramanian: I can start on this one. I would say that the literature would show that failure of other treatments is not a requirement for treating patients with botulinum toxins. In fact, the literature is quite robust in supporting trying botulinum toxin first, as Dr. Kelly said, that the use of alternative medications is associated with a much lower efficacy and with an increased side effect profile.

And so, no other treatment would be considered failure. I would say the one thing is that there are some individuals who have primary hemifacial spasms from neurovascular compression at the root exit zone of the facial nerve, and they may undergo a microvascular decompression, and they may fail that. They may still have some degree of hemifacial spasm even afterward. And so, those individuals may still be good candidates for botulinum toxin treatment postoperatively.

Dr. Scott Trimas: Okay. All right. I have a question along those lines, though, and I hate to deviate from the normal questions, but my question is, if a patient had, for example, an acoustic neuroma surgery or something else in the cerebellar pontine angle, and because you briefly kind of alluded to this when you talked about microvascular decompression, if someone had that, is there a time period you should wait after surgery - let's say they develop hemifacial spasms within X amount of time after the procedure, several weeks, several months, should you wait any period of time before instituting a botulinum toxin therapy?

Dr. Prem Subramanian: I can respond to that again. I would say that the development of the hemifacial spasm usually takes some time after. So, these are two separate things, right? The increase in the facial nerve that may occur leading to hemifacial spasm, as opposed to the pathophysiology of most so-called primary hemifacial spasm, which is also the vascular compression.

So, talking about these secondary cases where there is a development after a procedure, I'm not aware of strong evidence that would set a specific time point after which recovery would not be expected, or spontaneous regression would not be expected, and there are no clinical guidelines I'm aware of, but I would say that standard clinical practice would be that if the hemifacial spasm

is present for more than four to six months and has not remitted, then that is certainly a reasonable time point to try a single injection of botulinum toxin and there may be a benefit to the patient to giving that single injection and then waiting longer than the typical retreatment period to see if that single injection was sufficient to get them through an acute or subacute phase and that there might be some spontaneous regression of the symptomatology.

Dr. Scott Trimas: Okay. Thank you. So, question number three, what objective criteria scale should be used to measure treatment benefits and outcomes of hemifacial spasm with botulinum toxin?

Dr. Prem Subramanian: I'll let someone else start if they'd like.

Dr. Kelly Andrzejewski: So, I mean, there is - it looks like an actual approved, like validated hemifacial spasm grading scale, but this isn't something that, I'll be honest, I typically use in clinical practice. I think it's a clinical diagnosis that it's observed, and it's bothersome to the patient that there's treatment.

Dr. Prem Subramanian: Yes. I think the way the question is phrased does not really match what is in clinical practice, and it may be more relevant to any sort of clinical trial or clinical research that's being done to evaluate the efficacy. So, these hemifacial spasms scales, I also don't use them and have not seen them presented at neuro-ophthalmology meetings in terms of measurement of outcomes of treatment more broadly of patients with hemifacial spasms.

So, one of the drawbacks, I think, of these hemifacial spasm scales is that they center very much upon objectively observed spasm of the upper and lower face and the frequency and duration of those spasms, but those may not correlate with actual quality of life effects of the hemifacial spasm and the

improvement or lack of improvement with treatment or no treatment that the patient may experience.

Dr. Scott Trimas: Okay, thank you. All right. For any - question one, these are general questions regarding the botulinum toxin for use in facial - hemifacial spasms. So, for any condition, is there literature to support using a different dose other than the one approved by the FDA?

Dr. Kelly Andrzejewski: I think, again, in this case, it's really - I would typically - I mean, it's a bit of an art. You have to look at the patient, clinically determine what components of the hemifacial spasm are bothersome. Is it more forehead? Is it more the lower half of their face? And from there, decide on dosing. Again, I would start with a recommended FDA dosing, if not lower, depending on the patient. And then from there, you know, escalate the doses needed, depending on the patient's response to treatment.

Dr. Scott Trimas: Okay. What about off-label uses of different - like off-label uses for the different botulinum toxins? Is there any variation between effects?

Dr. Prem Subramanian: There are some. Yes, I mean, there's some head-to-head studies suggesting that there's not an effect - a difference in effect, other than, as was alluded to before, that you have to adjust the dosing for certain botulinum toxins that are not equivalent to onabotulinum toxin in terms of units, but there are - I'm not aware there - there's some literature that suggests that onabotulinum toxin or incobotulinum toxin may be superior to the others, but it doesn't mean the others don't work. There's evidence for each of those to show that they work.

Dr. Scott Trimas: So, there's obviously a dose-response relationship of the different botulinum toxin injections and the dosage that's used. So, I don't want to repeat that

question per se. So, how about frequency intervals? Is there evidence to support limitations on frequency intervals and total treatment durations?

Dr. Kelly Andrzejewski: I mean, I think, again ...

Dr. Prem Subramanian: Yes, go ahead, Kelly.

Dr. Kelly Andrzejewski: I think, again, in this case, it would be - depending on the patient's response, you know, I would typically see them back at six, eight weeks to determine if they had a response, that they're still getting benefits and plan for the normal 90-day interval. And if they come back and see me at 90 days and say, hey, my Botox wore off at 10 weeks, then you would request prior authorization to try to get approval for more frequent dosing, unless you thought that you should escalate the dose.

And it's really following patients over time, and every patient can have a different response. Some people have a response for eight weeks. Some people might have a response for 12 weeks. It just depends on the patient and their body.

Dr. Prem Subramanian: And then I'll just add for total treatment duration, again, in terms of evidence, there are retrospective studies for 10, 15 years showing that there's continued efficacy. There's not necessarily - you may need to escalate dose a little bit over time, but that the treatment - total duration between dosing probably stays about the same as Kelly just said for a given patient.

And that - I would say that limitations for treatment would be that if it's becoming less efficacious and either the dose has increased significantly or the duration between injections is shortening, that may be a time to consider a surgical alternative rather than continuing with the botulinum toxin injections.

(Stephanie): We're at five minutes.

Dr. Scott Trimas: All right. Would that also justify changing serotypes? In other words, if it had a limited duration of effect with one botulinum toxin serotype, would that justify changing to a different serotype?

Dr. Prem Subramanian: I'd say there's limited evidence on that, but it is a reason to consider switching based on some evidence that certain of the formulations are more or less immunogenic than others, or may have a slightly different mechanism of inactivation.

Dr. Kelly Andrzejewski: And I would agree with that.

Dr. Scott Trimas: All right. Okay. I don't think there's any necessity of body testing since it's already been questioned with that one. As far as, are there any contraindications for that? And along that same line, are there any long-term lingering effects that need to be taken into consideration for continued treatment with the botulinum toxin injections for facial dystonia?

Dr. Prem Subramanian: So, you want to start?

Dr. Kelly Andrzejewski: Yes. I think just, you know, knowing that people can have facial drip from, obviously, the Botox, but that would typically wear off with the - as the effects of the medication or the Botox wore off (unintelligible).

Dr. Prem Subramanian: And I think I mentioned already that these studies of patients 10, 15 years and beyond, have shown good long-term efficacy with repeated dosing, of course, but continued efficacy in most patients without significant adverse events and, in fact, the typical adverse events of using botulinum

toxin like ptosis or dry eye actually go down over time when you look at these studies.

Dr. Scott Trimas: Thank you.

Dr. Ola Awodele: Thank you, Dr. Trimas, and Dr. Kelly, Dr. Yang, Dr. Subramanian. So, Dr. Kelly, you stay on, and Dr. Kettler will join you for the discussion of cervical dystonia. Dr. Kettler?

Dr. Bob Kettler: Thank you, Dr. Awodele. Good afternoon, Dr. Kelly. I'm going to ask this first question a little differently than it's printed here, but I think it gets to really the same information. And, you know, what I'd like to hear you discuss is what type of documentation should our reviewers look for to determine that is actually the appropriate diagnosis for that patient?

Dr. Kelly Andrzejewski: I mean, I think kind of the classic cervical dystonia rating scale or the TWSTRS scale is really kind of the gold standard for the grading and diagnosis of cervical dystonia. I mean, it's very easy though, I mean, in my clinical practice to describe, you know, the components of retrocollis, enterocolitis, tilt, turn, rotation, things like that, and I think an accurate description of that within the physician's note that is used to request tyrosine should be sufficient, but in the same respect, if you're looking for a clinical grading scale, I would probably go with the TWSTRS scale, which is the Toronto Western Spasmodic Torticollis Scale, if I have the abbreviations correct.

Dr. Bob Kettler: Okay. You know, are there other scales that people use to document the severity of the cervical dystonia?

Dr. Kelly Andrzejewski: I mean, you could use the Unified Dystonia Rating Scale, but I think for the use of - you know, for grading specifically cervical dystonia, that's probably the best one.

Dr. Bob Kettler: Okay. All right. Would you use that then for measuring the treatment effect? I guess jumping ahead to question four.

Dr. Kelly Andrzejewski: I would say yes. In addition - so part of the TWSTRS scale, there's also kind of patient-reported outcomes, but it's not something I think in clinical practice we have time to necessarily have every patient fill out surveys rating the severity of their cervical dystonia. I think asking the patient's input on what they thought, if it was beneficial or not, is generally sufficient.

Dr. Bob Kettler: Okay. Is there a degree of regression in that TWSTRS scale that you think would support doing an early Botox injection or re-injection?

Dr. Kelly Andrzejewski: Meaning like at eight weeks instead of 12 weeks?

Dr. Bob Kettler: Yes. Yes, that's a common situation we face where it seems like patients are getting the injections earlier and earlier and other than, you know, a comment that the patient feels it's wearing off, there's not much there. Again, what should we be looking for to support doing it early?

Dr. Kelly Andrzejewski: I mean, I think the patient-reported outcomes, meaning the patient actually saying, yes, I feel like it's wearing off early is really the best indicator, because the ability of a physician to see a patient frequently enough, say, you know, every four to six weeks to actually grade them can be kind of challenging in my opinion and hard, especially if patients live a significant distance away and may or may not have access to telemedicine, you know, capabilities.

So, I don't know if that's kind of what you're looking for, but I think you really have to listen to the patients and the physicians. Patients don't want to get injected every six weeks if they don't need to.

Dr. Bob Kettler: Okay. All right. And do you consider botulinum toxin injections to be a first-line treatment for cervical dystonia?

Dr. Kelly Andrzejewski: Yes.

Dr. Bob Kettler: What are some of the other treatments that people might try, or is there no point in trying other treatments?

Dr. Kelly Andrzejewski: Potentially medications like muscle relaxants or benzodiazepines. But like I said earlier, all of these medications can have sedating effects or other problems that patients can encounter versus by injecting Botox, you're specifically targeting the problem itself, meaning in the neck, and you can kind of tailor, depending on what the patient's components of cervical dystonia is tailored to the specific patient.

Alternative to that would be something like deep brain stimulation, but that would be if botulinum toxin injections typically have failed or for some reason if the patient could not have Botox injections for some reason.

Dr. Bob Kettler: Okay. You know, one of the things, again, that we often see is that practitioners will rotate among the different Botox preparations. Is there any benefit to doing that or is it better to stick with one preparation for a course of therapy?

Dr. Kelly Andrzejewski: I mean, I think if the patient is reporting either earlier wearing off of the botulinum toxin and switching brands or types is certainly reasonable, but it can be kind of challenging to have to rotate, you know, from Xeomin to Botox to Dysport back and forth because of the differences in, you know, unit dosing, meaning like, yes, Xeomin and Botox are essentially a one-to-one, you know, equivalent, but Dysport to Xeomin or Dysport to Botox is more - can be like more of like a one to three, meaning for every one unit of Botox brand would be roughly three units of Dysport.

But there's, again, variable, you know, literature suggesting that that can be variable. So, I try to pick one and stick with it as long as the patient's getting a response, unless they're finding that they're consistently wearing off, say, at six or eight weeks, then I might switch brand initially before - you know, if I can't go higher on the dose.

Dr. Bob Kettler: Okay. Could we go to the next slide, please? Trying to - I think some of these, we've kind of gone over with some of our other conditions. And, you know, looking at these, I don't know that there's necessarily anything new to say here. Do you think that if people give the injections at more frequent intervals, that that plays a role in developing resistance to the injections?

Dr. Kelly Andrzejewski: No, I don't think so.

Dr. Bob Kettler: Okay. All right, thank you.

Dr. Kelly Andrzejewski: Thank you.

Dr. Ola Awodele: All right, thank you, Dr. Kettler. So, Dr. Kettler, and Dr. Kelly. Dr. Kettler, you stay on, and Dr. Chau.

Dr. Pham Chau: Pham.

Dr. Ola Awodele: Sorry, Pham. Dr. Pham.

Dr. Pham Chau: Pham. Yes.

Dr. Ola Awodele: Dr. Yang, and Dr. Subramanian will go on. So, I apologize. I think we switched your name on the slide, so sorry about that.

Dr. Pham Chau: That's okay.

Dr. Ola Awodele: With (unintelligible).

Dr. Bob Kettler: Okay. And, you know, I guess the first two questions here are sort of related in terms of whether Botox would be a first-line treatment or other things that should be tried first and failed. And maybe I'll start with you, Dr. Pham. Could you just discuss the issue of whether there are other treatments that should be tried, or if Botox really is the first-line treatment for blepharospasm?

Dr. Pham Chau: I would say that Botox should be the first-line treatment. There are really no other good treatments with as much even evidence as Botox has to treat blepharospasm to be used prior to trying Botox.

Dr. Bob Kettler: Okay. Dr. Yang, do you agree?

Dr. Ola Awodele: I don't believe Dr. Yang is on, actually. So, it's Dr. Subramanian and Dr. Pham only.

Dr. Bob Kettler: Oh, okay. All right. Dr. Subramanian.

Dr. Prem Subramanian: Yes, I would agree. I think the evidence around using any other agent shows lesser efficacy and a worse side effect profile, in particular, any of the oral agents that have been tried, there have been good reviews of that. So, I would consider botulinum toxin to be first-line therapy for patients. When we're calling it blepharospasm, we're assuming that means benign essential blepharospasm.

It's prudent to look at the ocular surface and to treat any ocular surface disease for any reflex blepharospasm that may be present. But again, if it's predominantly benign essential blepharospasm, then absolutely botulinum toxin injection.

Dr. Bob Kettler: Okay. Dr. Subramanian, I'll stay with you for the next one. And, again, kind of like I asked Dr. Kelly, you know, what should our reviewers look for in terms of objective criteria to determine both the effect of the injection, and I guess also if the injection is wearing off, and it's time for another one?

Dr. Prem Subramanian: In clinical practice, as well as in clinical trials, the diagnosis really is one that's made clinically. The Jankovic scale or other scales that have been developed can be used to try to assess or characterize the severity of the disease, but that's not done so much in clinical practice.

We tend to characterize it by mild, moderate, or severe spasm, and those scales also don't get at functional impairment like inability to read, inability to drive, and those are I think criteria that are used to measure treatment benefits in individuals who are given botulinum toxin for their blepharospasm.

And as far as the determination of the interval for dosing and when re-treatment needs to be done, oftentimes, again, from a clinical perspective, that

is done based on return of symptoms, return of difficulty with social interactions, reading and driving, and it correlates very strongly with objective observation of forceful eyelid closure and maintenance of that eyelid closure for more than a brief moment. Those two things go hand in hand.

So, I think when reviewers are looking at reports of a need for repeat treatment or perhaps even a shortening of the interval between treatments, those are the kinds of data that are reasonable to justify repeat treatment, perhaps even increased dosing, or a shorter interval between treatments.

Dr. Bob Kettler: Okay, Dr. Pham, what are your thoughts on that?

Dr. Pham Chau: I completely agree. I don't really have a whole lot to add, basically. I think most clinicians grade some kind of spasm severity by either saying mild, moderate, or severe, or using the Jankovic scale 1 plus, 2 plus, 3 plus, 4 plus, and then combine that with patient-reported symptoms, such as photophobia, inability to read or drive, interruption of, you know, activities of daily living.

Dr. Bob Kettler: Okay. The next question, I think what that's getting at is, are there specific areas that you can support providing an injection? Should it be limited to particular areas? Again, we sometimes see where there are, you know, injections done in quite a number of places that don't always seem to make sense for the condition. Dr. Pham, I'll start with you.

Dr. Pham Chau: So, just to clarify your question, you're asking about, like, the muscles into which the toxin is being injected?

Dr. Bob Kettler: Yes.

Dr. Pham Chau: Or are you talking about number four here, the finite number endpoint toxin injection question?

Dr. Bob Kettler: No. I was asking about the muscles.

Dr. Pham Chau: So, you're talking about the nine essential blepharospasm. I know that the package inserts specifically say something about the orbicularis muscle. However, there's been multiple papers in the literature that talk about other sort of periocular muscles that are involved in producing the blepharospasms that's observed.

So, you know, I think it's reasonable to include any and all periocular muscles that would be involved in eyelid closure, including, but perhaps not being limited to, the pretarsal orbital - preceptor orbicularis, the corrugators, the Perseus muscles. And, you know, there are a subset of these blepharospasms - benign essential blepharospasm patients that do demonstrate spread of spasm to like a Meige syndrome or, you know, where the spasm actually starts to involve more of their lower face as well. And in which case, you know, you're going to have to start injecting some of the other muscles of the face as well to get an adequate response.

Dr. Bob Kettler: Okay. Dr. Subramanian?

Dr. Prem Subramanian: I would definitely support that and say that it is a matter of individualizing the treatment for a given patient, because some patients will have very strong frontalis procerus corrugator spasms that will constrict the periocular area in such a way that it forces the eyelids closed, even if botulinum toxin is administered just to the orbicularis oculi.

And if you look at studies that have been done looking at the co-activation of that entire muscle system, it is clearly involved in this dystonia. So, it just needs to be tailored. And as she mentioned, there are certainly numerous studies that have looked at the benefits of injecting muscles other than those of the pretarsal orbicularis oculi.

Dr. Bob Kettler: Okay. We've kind of mentioned a little bit about injections at earlier intervals than what the package insert might describe. Do most patients last for about three months or are there a significant number of patients who require early injections? Dr. Subramanian?

Dr. Prem Subramanian: I would say the literature, as well as my own experience, would support that the majority of patients are able to go with the standard package insert type of interval between injections, but that some individuals, particularly those who may have another predisposing factor, I have a cohort of patients with tardive dyskinesia, for example, resulting in blepharospasm, they seem to potentially require higher doses and more frequent dosing than those who truly have a essential blepharosphasm.

Dr. Bob Kettler: Okay. Dr. Pharm.

Dr. Pham Chau: I would agree. Yes, I would agree. I have similar sort of findings where the majority of patients, you know, do fine with the standard interval and standard dosing, but there's a subset of patients, not only in the literature but also in my clinical practice, I would say up to 25% that would benefit from either more frequent dosing or higher dosing.

Dr. Bob Kettler: Do you think that more frequent dosing predisposes to resistance?

Dr. Pham Chau: No.

Dr. Bob Kettler: Okay.

Dr. Prem Subramanian: No, I've not observed that either.

Dr. Bob Kettler: Okay.

Dr. Pham Chau: And the literature doesn't back that up either. There is a recent meta-analysis of development of neutralizing antibodies in patients getting toxin, and ultimately the rate of antibody formation was incredibly low. And in addition of those patients that developed antibodies, most of them actually, it did not make them resistant to toxin effects. So, there is - you know, based off of that, I would say there is very little risk and little clinical significance to those.

Dr. Bob Kettler: Okay. All right. You know, I guess a question I would ask the two of you as well is the issue of switching amongst the different preparations. Is that a good thing, a bad thing? What are your thoughts on that?

Dr. Prem Subramanian: I can start on that. There have been head-to-head studies that have been published showing that you generally don't need to switch, but if you do switch between, in particular, onabotulinum toxin and incobotulinum toxin, that the effects in a given patient does tend to be pretty equivalent. Switching is, like in the other conditions we've talked about, generally done if there is a concern that there may be a decrease in efficacy and there is some literature to suggest that switching can restore response to the medication.

But I would say that it's not necessary in many patients, but it occurs for various reasons that may have something to do with the clinical issue or something to do with the administrative

Dr. Bob Kettler: Okay. Dr. Pham?

Dr. Pham Chau: I agree. Nothing to add.

Dr. Bob Kettler: Okay. Thank you.

Dr. Ola Awodele: Thank you very much, Dr. Kettler, Dr. Pham, and Dr. Subramanian, but you guys are going to continue with strabismus.

Dr. Bob Kettler: Okay. And I guess I'll start with Dr. Pham then. Is there evidence to support botulinum toxin injections as a first-line treatment for strabismus?

Dr. Pham Chau: So, I'll say the short answer is yes. However, I think there's a couple of weaknesses here, which is, number one, there's very few like large-scale Level 1 studies on it. Number two, most of what's out there is on a very specific type of strabismus, which is a comitant, non-paretic, non-restrictive etiology, which really doesn't encompass all potential indications and etiologies of strabismus, right?

So, there's, you know, restrictive strabismus. There's acute acquired paralytic strabismus. There's, you know, consecutive postoperative strabismus. There are like neuromuscular strabismus, neurogenic, iatrogenic strabismus. So, you know, the medium answer is, it likely depends on the etiology of the strabismus and really the primary, like, the clinical goal or endpoint that's desired with the use of the toxin.

Dr. Bob Kettler: Okay. Dr. Subramanian?

Dr. Prem Subramanian: Yes. The only thing I would add to that is that there is some evidence for using it in the treatment of acquired acute paralytic strabismus to

increase functionality in the short-term, may not affect long-term outcomes. And as Dr. Pham said, the vast differences amongst the conditions and the fact that sometimes we're talking about most of the studies actually being done in a pediatric population as opposed to an adult population, there are different considerations around using botulinum toxin as first-line versus some other therapies such as surgery or optical devices.

Dr. Pham Chau: Yes, I agree. And also, I just - I wrote some notes down here that there - I did find one Level 2 study that indicates actually better outcomes with Botox or with botulinum toxin in kids with a partially accommodative esotropia or a high ACA ratio esotropia. And so, specifically for that indication, there is definitely some evidence that says that botulinum toxin would be a good first-line treatment for that.

Dr. Bob Kettler: Okay. All right. I think we've really covered question two then in part of answering question one. And I think that covers it. Thank you both. Ola, I'll turn it back to you.

Dr. Ola Awodele: Okay. You're not going to go through any of the general questions at all? Or you're good with it?

Dr. Bob Kettler: I think, like, we've covered them. I guess I'll ask our experts, is there any of these questions that would be different for strabismus than conditions we've discussed already?

Dr. Prem Subramanian: I would say that one difference is that if you look at the evidence and treatment strategies around botulinum toxin for strabismus versus the dystonias like we've been talking about, the number of injections that are delivered is typically going to be far fewer for strabismus than for other conditions, because if you are temporizing a patient with an acute acquired

condition that may ultimately resolve, then the botulinum toxin is useful with one or two injections.

And similarly, the literature around childhood strabismus suggests that some patients may respond to a single therapeutic injection of botulinum toxin, whereas others may require repeat therapy. So, there are some different issues around dosing and interval that have to be determined clinically by the treating physician.

Dr. Pham Chau: Yes, I would agree with that. There is a potential for an endpoint, you know, particularly if you're trying to treat, you know, like an acute paralytic etiology that might resolve eventually, there - you know, I think the difference here is that there might actually be an endpoint to treatments at some point.

Dr. Bob Kettler: Okay. Thank you. Ola?

Dr. Ola Awodele: Yes. Thank you very much, Dr. Kettler, Dr. Pham, and Dr. Subramanian. And before we move on to the next one, Dr. Ferzandi joined us, and I would like to have her check out her audio just to make sure everything is good before she gets to her topic. So, Dr. Ferzandi, could you please introduce yourself and tell us your affiliation?

Dr. Tanaz Ferzandi: Sure. Can you ...

Dr. Ola Awodele: Your affiliation, and any ...

Dr. Tanaz Ferzandi: Can you hear me?

Dr. Ola Awodele: Yes, we can hear you.

Dr. Tanaz Ferzandi: Okay, good.

Dr. Ola Awodele: And any conflicts of interest, if they exist. Thank you.

Dr. Tanaz Ferzandi: Sure. I've been on the entire time since 10:30. There's just been something wrong with the audio. So, I'm Tanaz Ferzandi. I'm the University of Southern California urogynecologist, and along with Dr. Amy Park, representing the American College of OBGYN and also the American Urogynecological Society. I have no conflicts of interest.

Dr. Ola Awodele: Thank you, Dr. Ferzandi. Okay, we'll go on with the meeting to chronic migraine prophylaxis with Dr. Moynihan, Doctors Monteith, and Knight. So, Dr. Moynihan, over to you.

Dr. Teshamae Monteith: Hi. Great. Thank you.

Dr. Eileen Moynihan: Yes, thank you so much for joining us. I think because we have a bunch of questions for this one, I'm going to ask one of you to answer first and then the other to add to it and maybe alternate that, starting with Dr. Monteith. Is there evidence to support treatment or treatments prior to using botulinum toxin injections for chronic migraine prophylaxis?

Dr. Teshamae Monteith: There's really not. It's not - there's no evidence for step therapy for using onabotulinumtoxinA for treatment of chronic migraine. There may be financial reasons, cost savings reasons. There are a number of other therapeutics that have efficacy for chronic migraine, Topiramate, which does have a significant adverse profile, anti-CGRP monoclonal antibodies.

There are four out on the market to the lichen or to the receptor, as well as Atogepant, gepant. These are the data. Generally speaking, insurance requires

trials of oral therapies that have very little evidence for chronic migraine, which is more burdensome and associated with more headache days.

Dr. Eileen Moynihan: Thank you. Dr. Knight, do you have anything to add?

Dr. Sonya Knight: I agree with the statement. I would just add that when you look at the research, the Botox is pretty equivalent to other by-mouth medications that are on the market and even the injectables. And the thing is, is that when you look at the studies, the dropout of patients on a lot of the by-mouth medications is pretty significant. And so, I really agree that it should be considered head-to-head with other possible treatments.

Dr. Teshamae Monteith: I'm not sure I understood that comment. There's very little evidence for the oral therapeutics for treatment of chronic migraine.

Dr. Sonya Knight: No, no, no. What I'm saying ...

Dr. Teshamae Monteith: With the exception of Topiramate.

Dr. Sonya Knight: Yes, no, but what I'm saying is, and Amitriptyline is also one that we see in the literature, but what I'm saying is ...

Dr. Teshamae Monteith: Not for chronic migraine.

Dr. Sonya Knight: Not for chronic, but Topamax is still - if you look at the studies, the dropout rate of people on Topamax compared to Botox is pretty significant ...

Dr. Teshamae Monteith: I agree.

Dr. Sonya Knight: ... when you look at the actual studies.

Dr. Teshamae Monteith: Absolutely. So, the problem is the tolerability of Topiramate is problematic for many patients.

Dr. Sonya Knight: Correct.

Dr. Eileen Moynihan: Thank you. Starting with Dr. Knight, is there evidence that supports the need for concurrent use of other medications in addition to botulinum toxin injections for chronic migraine?

Dr. Sonya Knight: Yes. Actually - there are actually some nice studies that are coming out now specifically with Botox along with the CGRP medications, using them concurrent and showing that there is more efficacy with the two of them together. So, I definitely think that there is some evidence in the literature that is supporting concurrent treatments.

Dr. Teshamae Monteith: I agree with that, and in addition, it makes biologic sense because they have different mechanisms of action.

Dr. Sonya Knight: Yes.

Dr. Eileen Moynihan: Great. Thank you. Dr. Monteith, does the evidence point to specific criteria that should be used to measure the treatment benefits and outcomes of chronic migraine prophylaxis with botulinum toxin?

Dr. Teshamae Monteith: I think that we need to think about patient-centric approaches, and the issue is that some patients may respond in terms of headache days, 50% responder rates, but other patients may respond in a reduction in moderate to severe days that might be significant for them. Some patients may have the

same number of total headache days or migraine days, but there's a 30% reduction in pain intensity.

So, I think that you have to look at a number of patient-reported outcomes to determine whether it's efficacious or not, because we know migraine is a heterogeneous disorder, and patients may respond in different ways.

Dr. Eileen Moynihan: Dr. Knight, anything to add to that?

Dr. Sonya Knight: No, that was well put.

Dr. Eileen Moynihan: Okay, Dr. Knight, is there evidence to support at least a 50% reduction in meeting headache days per month when using botulinum toxin for chronic migraine?

Dr. Sonya Knight: Yes, there is. Yes, there is. I think there's plenty of evidence now, whether it be PREEMPT or other studies that definitely does show this.

Dr. Eileen Moynihan: Anything to add, Dr. Monteith?

Dr. Teshamae Monteith: Yes, I think a 50% responder rate is an important outcome measure, and it's something that we're trying to look at across therapeutics. But if patients have 30% response rate for specific patients, that might mean keeping their job versus not keeping their job.

Dr. Eileen Moynihan: Understood. So, Dr. Monteith, knowing that FDA reviewed the PREEMPT studies results and only approved onabotulinumtoxinA at 155 units, is there robust evidence demonstrating that more than 155 units of onabotulinumtoxinA is clinically superior and more effective when treating chronic migraines?

Dr. Teshamae Monteith: For patients that are non-responders to 155 units, it makes clinical sense to increase the dose to 195 units, and that's done in other countries or European colleagues. And there's a number of observational studies that have shown that follow-the-pain larger dose may actually provide a better response rate.

Dr. Eileen Moynihan: Dr. Knight?

Dr. Sonya Knight: I agree. Even in the PREEMPT trial, they actually did allow for an extra 40 units, and they were following the pain. And when you look at the results, they're saying that it's just as safe, and it's well-tolerated. So, we need to treat our patients for their needs, and we should have the availability to be able to provide that, especially when research is saying that there's no need not to.

Dr. Eileen Moynihan: Thanks. Dr. Knight, knowing the FDA reviewed the PREEMPT results and only approved onabotulinumtoxinA to be administered every 12 weeks, is there robust evidence demonstrating that less or fewer than 12 weeks dosing of onabotulinumtoxinA is clinically superior and more effective for treating chronic migraines?

Dr. Sonya Knight: So, I think we kind of covered this a little bit because the question of the 12 weeks really has to do whether over time there's any reduction in the efficacy if we go to the less than 12 weeks, but a lot of the research is showing that that is not the case. And I think it's just a very individual thing because there are a lot of patients who will come to you who are winding up running out of the efficacy of the medication sooner.

So, I think that the literature is really showing us and speaking to the idea that there is not necessarily the reason not to administer every - has to be on point

at every 12 weeks and always thinking about doing the most effective for the patient.

Dr. Eileen Moynihan: Dr. Monteith, anything to add to that?

Dr. Teshamae Monteith: Yes, I agree with this statement that every 12 weeks is an average. There are patients that require more frequent injections because there is wearing off. So, while there's not randomized clinical trials comparing every eight weeks to every 12 weeks for chronic migraine patients, there's a number of real-world and clinic-based studies that are consistent with, I think, a clinical experience that wearing off can be significant for some patients as early as eight weeks, other patients as early as 10 weeks, and so that more frequent dosing may be indicated for certain patients without the concern of increased adverse events.

Dr. Eileen Moynihan: Thank you. For this condition, what might determine a safe dosing range? Just the studies or?

Dr. Teshamae Monteith: Dosing range or frequency?

Dr. Sonya Knight: Yes.

Dr. Eileen Moynihan: Dosing range.

Dr. Teshamae Monteith: Yes, so we don't really - I mean, that's a great question. It would be nice if we had predictors. We don't have predictors. So, it's really based on lack of efficacy, and I think it's based on lack of efficacy, and there may be other things that people may consider, but generally speaking, it's lack of efficacy.

The patient doesn't respond to 155 units, it makes sense to increase to 195, and again, in some clinical practices, they go straight to the 195.

Dr. Sonya Knight: Absolutely.

Dr. Teshamae Monteith: I would just also like to add that the earlier studies, the complication rates of using onabotulinumtoxinA for treatment of chronic migraine, seemed to have been much higher neck pain. I think that they've - over time, the field has done a good job of learning the best practices for injecting both small muscles and large muscles and preventing some of those complications. So, it's really not much of a concern. And also, identifying patients that have preexisting weakness that you wouldn't want to go higher on.

Dr. Eileen Moynihan: Okay, thank you. Is there any evidence considering chronic migraine to support any limitations of treatment duration for this condition? And what I mean is, could you control it so well, let's say even with a combination therapy that you then drop out of the definition of chronic migraine, or would you say about chronically treating the patient, once you make that diagnosis, you're always going to treat it? I hope that's ...

Dr. Teshamae Monteith: Great question. I don't know who you want to take that question, but it's a great question.

Dr. Eileen Moynihan: You can both take a stab at it. I wasn't sure - I mean ...

Dr. Teshamae Monteith: I think - I feel like that's what we're doing. We're taking a stab at it. There are clearly patients that have - and then we have to look at the analogies, depression, anxiety, schizophrenia, a patient that has schizophrenia

that's on antipsychotic medications and is no longer having hallucinations or, you know, psychotic, does that person still have schizophrenia? Yes.

And so, the problem with chronic migraine, and some people even beyond the scope of this call debate that chronic migraine should exist, that migraine is just migraine, and there are higher frequencies of migraine and lower frequencies of migraine. Having said that, we don't have a way to gauge whether someone - whether you pull the medicine away, whether they will relapse back to that higher frequency, or as we know, that migraine is also a relapsing, remitting kind of condition, where patients can go through periods of doing well, even without medication, and doing worse.

So, we don't really have a way of knowing when we stop these medicines. There's certainly people and possibly indicators that you could hold medication on a patient and if their frequency increases, restart the treatment. But there's no way to guide that decision-making.

Dr. Sonya Knight: Yes, I completely agree, and I think that, you know, that's one of the things working with our patients to be able to recognize if they have reentered into their migraine patterns because there are a lot of different things that can cause that to happen. So, I completely agree.

Dr. Eileen Moynihan: Thank you. Is there evidence to support using a different botulinum serotype interchangeably in the absence of an individual FDA approval for this condition?

Dr. Teshamae Monteith: There's not evidence. You know, there may be places where access is an issue, but we really don't have evidence to support the use of other neurotoxins for treatment of chronic migraine. That may change because I'm

aware, and it's in the public space of other, you know, trials coming down the line, but we just don't have the evidence.

Dr. Eileen Moynihan: Okay, thanks.

Dr. Sonya Knight: Yes. I am ...

Dr. Eileen Moynihan: Oh, did you want to say something and add to that, Dr. Knight? I'm sorry.

Dr. Sonya Knight: Oh, no, no. I just agree. I just agree.

Dr. Eileen Moynihan: Okay. I'm guessing the answer to the role of antibody testing is the same for this as it was for the other conditions. It's not something that you necessarily need to do or?

Dr. Teshamae Monteith: Yes.

Dr. Sonya Knight: It is similar. It's not going to make a difference as we had talked about before in migraine versus some of these other treatments using Botox.

Dr. Eileen Moynihan: I heard you mention that if the patient already was somewhat weak, you might not want to use this approach to treatment, but what are the contraindications that exist for the use of botulinum toxin in this entity?

Dr. Sonya Knight: Well, besides like motor weakness, of course, you'd also, like if somebody has some major skin issues, you know, those are not areas that you could be injecting Botox into. If you already had somebody not only like who also has swallowing issues, talking issues, breathing issues, you know, any of course allergy to Botox and stuff like that, so those would truly be limiting factors,

but it wouldn't - if you had skin conditions, it doesn't mean that Botox could not be used in areas where you did not have such inflammatory skin issues.

Dr. Eileen Moynihan: Anything to add to that, Dr. Monteith?

Dr. Teshamae Monteith: Yes, so neuromuscular disorders, neuromuscular junction disorders specifically, not just like general weakness, and I agree, there's like a herpetic lesion, you may not want to inject. If there's someone that has an active Bell's palsy that's an acute, you may not want to inject, but there's very little contraindications to injecting.

Dr. Sonya Knight: Absolutely.

Dr. Eileen Moynihan: Are there long-term effects of botulism toxin in this entity of chronic migraine?

Dr. Teshamae Monteith: It's not well captured. I mean, there's certainly potential cosmetic side effects that most patients don't mind, surprisingly. You know, for example, temporalis muscle can look thin and that can be cosmetically unpleasing, but beyond that, no.

Dr. Sonya Knight: Yes. And I agree with that completely.

Dr. Eileen Moynihan: Okay. Well, thank you very much. I think this concludes this section, unless any of the other medical directors have any additional questions.

Dr. Ola Awodele: Yes. Thank you, Dr. Moynihan. I do have one little thing to add in terms of questioning. When we're talking about evidence to support at least 50% reduction in the mean headache days per month, Is it reasonable to expect - what kind of documentation is one to expect in a note concerning the nature of

the headaches that the patient is having, you know, to support the fact that it is migraines as opposed to other types of headache? So, is there any evidence or what kind of documentation should we expect to see in the chart?

Dr. Teshamae Monteith: So, the standard documentation requirements is usually a history of chronic migraine and, you know, we use international classification of headache disorders now in its third edition, but, you know, it's a clinical diagnosis, so it might not go by that strict classification. But in order to meet the standards would be 15 headache days for at least three months, at least four hours in duration.

So, that's the standard documentation. And it's clinical. It's by clinical report. The 50% responder rate, while great, is not the only outcome that might be important to the patient or of value to the patient. So, there are disability scales like MIDAS that are sometimes used, patient diary information that is used. There's patient migraine-specific quality of life that can be used.

So, there are a number of indicators. And I think the patient simply saying they're better, a reduction in analgesic use is another example. So, I wouldn't fixate on a 50% responder rate as the sole kind of outcome measure.

Dr. Sonya Knight: I agree with that too. You know, quality of life is extremely important. And sometimes that 50% doesn't really get to that point of life quality as it could be.

Dr. Teshamae Monteith: It could also be associated symptoms. Patients can have less nausea and vomiting, you know. And so, migraine we know is more than just a headache and that there are these associated symptoms that matter as well.

Dr. Eileen Moynihan: Ola, are you still there?

Dr. Teshamae Monteith: Yes.

Dr. Ola Awodele: Sorry, I was saying, thank you very much. Thank you, Eileen. I had gone on mute while they were talking. I was saying, and it would be reasonable to expect, rather than just seeing something like, patient had only five headaches this month or something, it would be reasonable to expect a character, you know, the character of the headaches that the patient did have in the chart.

Dr. Teshamae Monteith: Well, I think if a patient went from 15 to 5, that's significant. The more it has research, the more documentation, the better, but we don't always get that. But I think that if you go from 15 to 5, that's a massive reduction, over 50% response for sure. So, I don't think you necessarily need that.

Dr. Ola Awodele: Okay, so then the last question I have is, so let's say this has happened, the patient keeps consistently having, let's say five headaches, right, have been getting it every 12 weeks. Is there literature, you know, to support or be prolonging when you - you know, a trial of prolonging the interval? You know, we talked before about reduce - you know, the reduction in interval, but is there literature to support prolonging the interval, so longer than 12 weeks?

Dr. Teshamae Monteith: Yes. So, there's really not. For some patients, this is just in my clinical practice, I may have one or two that have had like two migraines per month, and we said, okay, well, let's stretch it out, let's stretch it out, and let's see if we can wean you off and what happens, and, you know, let's see if you can go four months, because they hate - maybe they hate the needle.

So, some people, and they're happy to go those four, and for some patients that might work, but there's really not clinical guidance to support doing that.

Dr. Sonya Knight: No, there isn't.

Dr. Ola Awodele: Okay. Thank you very much. Thank you. Thank you very much. So, next is myself and Dr. Gyawali, and we're going to be talking about anal fissure. So, Dr. Gyawali, are you unmuted?

Dr. Prakash Gyawali: Yes. Ready to go.

Dr. Ola Awodele: Okay. All right. So, is there any evidence to support the use of botulinum toxin injections as first-line treatment for anal fissure?

Dr. Prakash Gyawali: There actually is not. Anal fissure and the use of botulinum toxin is a little different from the other uses that we have talked about. So, anal fissures develop when there is some trauma to the anal canal, and the most common mechanism of that trauma is hard stool passing through. Once there is that trauma, since that area is extremely sensitive and there are sensory nerves, the response - there are two elements that happen in the response.

First is pain, because there is pain when stool passes through. The second is a reflex spasm of the sphincter muscle, usually the internal, but sometimes the external as well. Botulinum toxin is used to blunt that spasm. Sometimes the spasm can cause pain. So, clearly, it isn't necessary in every patient. Most anal fissures heal on their own if the stool is made soft so that it can pass through and the patient doesn't have to strain or have a lot of discomfort while allowing the stool to move through.

So, most anal fissures will heal with stool softeners and laxatives and sometimes use of topical muscle relaxants like nitroglycerin cream or calcium blockers that can be applied in the form of creams. Once in a while, topical

analgesic-containing creams can be applied to the anal canal. There are commercial preparations that have lidocaine and steroids in them.

The vast - vast majority of anal fissures heal with these treatments. Once in a while, the spasm is counterproductive or the pain is counterproductive in that the patient isn't able to evacuate stool because of how tight the muscle is going to close the lumen. And in those situations, botulinum toxin injection can help reverse that consequence of the presence of the spasm. So, the short answer is, there is no evidence to use botulinum toxin as the first line of treatment for anal fissure.

Dr. Ola Awodele: Okay. And I think you've kind of answered question two as well in terms of the treatment that should be tried prior to using botulinum toxin injection for anal fissure. Do you have anything else to add to that?

Dr. Prakash Gyawali: The only additional comment I would make regarding this is that sometimes the botulinum toxin helps with the pain of defecation. And so, if there is significant pain with defecation despite all the other measures, that by itself may escalate the need to use the botulinum toxin a little earlier in the management, not necessarily first-line, but a little earlier in the management.

Dr. Ola Awodele: Okay. Thank you. So, is there evidence to continue the use of botulinum toxin injections after the first two injections in anal fission?

Dr. Prakash Gyawali: There is no good evidence for a long-term or a repetitive injection pattern in that setting, because if the muscle remains at spasm and the fissure persists, there could be one of two possibilities. The first is that there is some other mechanism for the fissure, like the patient has Crohn's disease or some other reason for the fissure, and that needs to be investigated.

The second is the fact that not every patient responds to botulinum toxin, and that patient could be a non-responder. If you look at the literature, anywhere from 20% to 50% may not respond. And so, a decision will have to be made after two or three injections as to whether management needs to escalate to a sphincterotomy or a fissurotomy, depending on what the fissure looks like to the surgeon.

The only exception to the rule probably is going to be the pain patient, the patient with pain who has a very noticeable improvement in pain after botulinum toxin injection and the pain recurs because pain by itself can lead to recurrence or propagation of the fissure just because of how pain can create a situation of obstipation.

And the longer stool stays inside, the harder it gets. So, it gets into this vicious cycle of the patient not wanting to defecate. Stool becomes hard, and when they eventually defecate, that airs up the fissure a little bit more. So, that may be the one situation where it might make sense, especially if the fissure was healing or moving in the right direction to repeat an injection past the first two if there was a positive response to the earlier injections.

Dr. Ola Awodele: Okay. Thank you. So, I'm going to move on to general questions. I think I just have a couple. They're intertwined. So, is there robust literature to support using a different dose or a different frequency than the one approved by FDA?

Dr. Prakash Gyawali: The literature is all over the place in terms of dose and frequency. And so, if the question is, is there hard evidence to support a fixed frequency, injection frequency, there isn't, or a fixed dose, there isn't. Doses anywhere from a total of 50 to 100 units have been used, and it seems the response is not necessarily different when doses higher than 100 units have been used.

So, I would say that the adequate - the appropriate dose is somewhere between 50 and 100 units in divided doses. There is also no consensus in where exactly to inject. Most people agree that it's the internal sphincter that needs to be targeted either anteriorly or posteriorly. Some people inject into the fissure. Some people inject next to the fissure. The response seems to be the same regardless of where the injection is made.

Dr. Ola Awodele: Okay. Thank you. And the last one is, is there evidence to support using a different botulinum serotype interchangeably in the absence of individual FDA approval for the same - for anal fissures?

Dr. Prakash Gyawali: I think there is no evidence to suggest that that approach would not work. I'm answering your question in the reverse.

Dr. Ola Awodele: Yes, that's what I (gathered in your statement).

Dr. Prakash Gyawali: It will probably work, but there is no comparative studies. It might be reasonable to change the brand if the expected results have not reached. But, you know, it can't be supported with any of the evidence that I've reviewed.

Dr. Ola Awodele: Okay. Well, thank you very much. I think that's all, unless you have any other thing that you wanted to say about this?

Dr. Prakash Gyawali: I don't have anything more to say, but thank you.

Dr. Ola Awodele: Thank you, Dr. Gyawali. All right. So, coming up next is intravesicular analgesia by Dr. Loveless and Dr. Park.

Dr. Meredith Loveless: Hello.

Dr. Ola Awodele: Hi.

Dr. Meredith Loveless: So, we'll move into the - how are you? All right. So, what evidence, if any, supports the use of botulinum toxin injections for the off-label use for interstitial cystitis and/or bladder pain?

Dr. Amy Park: So, there are studies that look at this interstitial cystitis and bladder pain, and Botox is definitely a part of the algorithm for this. And the - I mean, in terms of cystitis, one of the characteristics is reduced compliance. So, Botox, by relaxing the detrusor muscle, does help with the urgency-frequency component of it.

Dr. Meredith Loveless: And how about evidence for the use for - off-label use for intravesicular vesicle analgesia?

Dr. Amy Park: Yes, this question I'm not quite sure of because the intravesicular analgesia, in my mind, is administering things like intravesical lidocaine or, you know, administering heparin. So, I think it does help with the bladder pain aspect, if that's what the question is ...

Dr. Meredith Loveless: Yes. I think it's asking, is there any role for injection of Botox for the analgesia component for IC, not necessarily the - just filling the bladder with the lidocaine heparin modality.

Dr. Amy Park: Okay. Yes, the thing about the botulinum toxin is that it does affect the afferent supply because, you know, if you look at, for instance, the overactive bladder and neurogenic bladder literature, the urgency frequency component is really like an efferent sensation problem. So, it does have these effects in terms of modulating the pain and the urgency component.

Dr. Meredith Loveless: And is there any evidence that it would support its use in that or is it more of a experimental trying to figure out if it would benefit at this phase?

Dr. Amy Park: This is something that I know is - many protocols are dedicated to using the botulinum toxin for the interstitial cystitis. Usually, those are performed in the operating room due to the patient's discomfort with just any kind of distension, bladder distension.

Dr. Meredith Loveless: Okay, thank you. And I believe you're going to be staying on for the next set of questions.

Dr. Ola Awodele: So, Dr. Loveless, do you want to wait till, do you think the general questions and kind of be lumped together?

Dr. Meredith Loveless: We can wait.

Dr. Ola Awodele: Okay. All right. So, we'll move on to the next set, yes. And we'll have Dr. Ferzandi join to answer our neurogenic bladder questions.

Dr. Meredith Loveless: Great.

Dr. Tanaz Ferzandi: Hi.

Dr. Meredith Loveless: Hello. Welcome, Dr. Ferzandi. The next question is, is there evidence to support the use of botulinum toxin as a first-line treatment for neurogenic for overactivity bladder?

Dr. Tanaz Ferzandi: So, there aren't any clear trials talking about that specifically, but when you look at most of the trials and also just clinical practice in general, I think a lot of people feel that using Botox in patients who have severe issues of

overactivity and have the underlying condition of neurogenic bladder, that they feel like it is the most efficacious.

And so, there are studies that have obviously - most of the studies are done in adult men, but there are some pediatric studies as well. And even those have shown high rates of efficacy over their long term. And when you look at patient satisfaction, et cetera, those also follow suit.

Dr. Meredith Loveless: Thank you. And what treatments, if any, would be considered failures prior to the use of botulism toxin injection? I think what the question's really getting at is, you know, what - we asked if it was first line, when would it be used as a second or third line option in the management of this condition?

Dr. Tanaz Ferzandi: Yes. So, it's interesting. When you look at some of the data, though, a lot of these - there's a confounder, right, because a lot of these patients have been tried on anticholinergic, more so the beta-3s that we have available. So, a lot of these patients in the trials also were tried on anticholinergic. And I think in clinical practice you will see that because a lot of times we are kind of driven to do that before we get approval for Botox in these patients.

So, again, I wouldn't necessarily say that we need to see these failures because a lot of us would feel that moving forward quickly is better for the patient, especially in our neurogenic patients who already have issues with recurring UTIs and more so with retention as their primary, you know, kind of qualifying symptoms.

Dr. Meredith Loveless: And then, two, you've already answered question three, but are there any guidelines that provide recommendations in this area? And then my other question was, is there issues with when you mentioned the retention, is it

- you know, what preparation or what considerations do you need to make in terms of if they have retention exacerbated by the botulism?

Dr. Tanaz Ferzandi: Sure. I think that's where you have to kind of look at the guidelines and then look at the clinical scenario. So, yes, there are guidelines from most of the societies that kind of work in this space talking about how Botox can be used in the therapy algorithm. I think when you talk about retention, most of these patients already have retention.

And so, when we talk about the - a lot of the studies look at either 200 versus 300 units used in the neurogenic bladder population. And so, the retention rate is higher in those patients anyway, but most of these patients are already self-catheterizing. And so, what we're trying to do is ameliorate the symptoms of severe detrusional overactivity where they're having leakage and, you know, the quality of life is pretty abysmal.

So, I mean, I think all of these questions kind of get smelted into one, frankly. And so, there is a lot of evidence in relation to the Botox for this population. And then, interestingly, you know, whether you use 200 versus 300 units, there isn't any robust evidence to say one dose is better than the other. But generally, we start at 200 and some people will go to 300, but the clinical data doesn't necessarily support the 300 dose.

And then there is some evidence to show that over the long term, at least in the pediatric population, there is a waning effect of efficacy after, you know, multiple years of using this.

Dr. Amy Park: I'm just going to jump in here and just say - this is Dr. Park. You know, there are AOA guidelines regarding using the botulinum toxin. And I do think that the 200 and 300 dose has been extensively studied in this setting. And I know

that clinically, just - I know there's always questions about the off-label use that some people even are using 400.

Dr. Meredith Loveless: Thank you. And then, Ola, are we moving to the next set on the overactive bladder, or?

Dr. Tanaz Ferzandi: Yes, I think we have three sections that we possibly could just kind of combine and see whether that might be more efficient.

Dr. Ola Awodele: Yes, I see that. So, (Stephanie), could you advance the slides, please?

Dr. Meredith Loveless: Great. Thank you. So, this will include both Dr. Ferzandi and Dr. Park. And so, the first question is, is there any off-label use for the botulism toxin for overactive bladder? If so, please describe. So, this would be beyond what's already been established and acceptable labeled use.

Dr. Amy Park: So, this is Dr. Park. I was just going to say that one thing that reading the packet ensures, and I think that the other panelists can also speak to this, but the dosage is technically - according to the insert, is not to exceed 400 units in three months. I will say that speaking with my neurology colleagues, they exceed this limit all the time.

Especially in the neurogenic population, it's - the timing of these doses in those patients who have multiple sclerosis and are getting their muscles injected, it's usually a high dose. And I think clinically, there's not really been any evidence of untoward effects as they exceed these limits all the time. I will say that although the FDA guidelines for the overactive bladder dosage is officially 100 units, dose escalation to 200 units has excellent results for those patients who have experienced partial or lack of response.

I'm just going to refer to this randomized controlled trial by Dr. Amundsen, et al., called the ROSETTA trial, and that randomized patients with refractory overactive bladder to botulinum toxin 200 units versus sacral neuromodulation. And this showed that they were equivalent. So, there's definitely - this was published in JAMA in 2016.

So, there's definitely evidence to support the use of 200 units in idiopathic detrusor overactivity. And like I alluded to before, there's - for neurogenic, there's definitely multiple studies looking at 200 and 300 units for neurogenic detrusor overactivity.

Dr. Meredith Loveless: Thank you very much, and also for the references. And the next set of questions are all really aiming at the same thing. Who's the right patient for Botox for overactive bladder? So, if we could go back to the overactive bladder slide, please. Thank you. And so, we're looking at what treatment should have been - is typically done prior to moving to botulism for treatment. Is there any evidence or established algorithms for that? And then also, is there a certain number of medications and classes that should be tried? So, we're really trying to look here at patient selection.

Dr. Tanaz Ferzandi: So, this is Ferzandi. I mean, I think it's really important to kind of break this down. You know, we have these algorithms that have been published, and I think a lot of people tend to follow them. I think it's really important for our clinicians to do the baseline treatments, and that is understanding behavior.

When we start throwing these medications and interventions at our patients, but they are excessively caffeinated, or they're drinking literally gallons of water a day, we're not going to be overriding it. So, I think the practical way of addressing this is to do the conservative management and behavior

management. If they have failed that, and if - you know your patients, and if they've really failed that, then I tend to be a little bit more aggressive.

I tend to look at the patient kind of in total. If I have an elderly patient who's already on multiple medications, and she can barely keep dry at night, she's waking up, all of these things that are a detriment to her overall well-being, we don't want her falling at night, et cetera, you kind of take that whole person in perspective. And I tend to be a little bit more aggressive in trying to get them to Botox.

We have other modalities available, which are nerve stimulators, but you have to kind of gauge whether or not the cost and the time that it takes to get these patients on board versus being able to offer them something in the office that is very low risk and very efficacious. And if I need to repeat a dose, I can do that as well.

So, I think when we look at like questions two, three, et cetera, I hesitate because a lot of times we feel like our hands are tied having to follow the step-by-step-by-step process, when we know that perhaps moving them along that algorithm would be beneficial to them.

Dr. Amy Park: Yes. I'll just add that the AUA-SUFU guidelines do say that - recommend behavioral modifications, oral antimuscarinic beta-3 agonists, and - but there are so many - the antimuscarinics or anticholinergics are problematic for those patients who are elderly, have polypharmacy. There's an associated risk of - increased risk of dementia with the use of anticholinergic medications.

And so - and then, you know, concern about gastric emptying because of the flowing of the bowels, like gastroparesis, et cetera. So, there's definitely - and overactive bladder is very common in this patient population. So, I think that

there is - regarding needing to try medications prior to proceeding with Botox in those populations can be problematic and cause more issues.

You know, it is also an issue for those who are - you know, the elderly also have a lot of polypharmacy. Regarding mixed urinary incontinence, I would definitely say that, you know, the urge tends to be more bothersome. So, we use patient-guided decision-making to counsel them. And if they choose to address their urge with a botulinum, it's a very efficacious therapy, as all of the other panelists have alluded to.

Dr. Tanaz Ferzandi: (As medics).

Dr. Meredith Loveless: Thank you. And our final question in this area is, again, dealing with patient selection, but you just addressed some of the concerns with the medication and potential effects it may have in this population. Are there any concerns directly related to the use of the botulinum toxin, such as anything that you might consider a relative or absolute contraindication in this population or higher risk for failure to respond?

Dr. Tanaz Ferzandi: Amy, you want to take that?

Dr. Amy Park: Yes. As previously alluded to by the panelists, the patients with like muscle weakness disorders like myasthenia gravis, Lambert-Eaton syndrome, you know, we should exercise caution. I think that clinicians just also need to be careful about patients who have a history of diabetes or those with a history of recurrent UTIs.

I will say, patients who have recurrent UTIs tend to get UTIs regardless, but just maybe having extra care regarding the peri-procedure antibiotic prophylaxis is helpful.

Dr. Tanaz Ferzandi: And I think I'll add that you have to be thoughtful about patients who are outright anticoagulated and how comfortable you feel doing these injections in the clinic versus in an outpatient center. I think those are just more logistical and operational things. That's not a contraindication, however.

Dr. Meredith Loveless: Okay. I appreciate your answer. And I believe that concludes this section. Oh, we've got the urinary incontinence. And then the evidence regarding the use of botulism toxin for urinary incontinence and the quality of that evidence.

Dr. Tanaz Ferzandi: There are several RCTs looking at the use of botulinum toxin for urinary incontinence. I alluded to the ROSETTA trial looking at botulinum versus sacral neuromodulation. The one prior to that, I think it's from 2012 in the New England Journal of Medicine, was the ABC trial. And this was performed by Dr. Visco, et al., basically showed that botulinum toxin is efficacious and results in the complete resolution of urgent incontinence in a high proportion of women, about a third of women as opposed to about 13% in those patients taking anticholinergics.

Dr. Meredith Loveless: And would your comments regarding conservative treatment and number of medications be any different for urinary incontinence than it was for overactive bladder, or do you feel that you would utilize the same approach in this population?

Dr. Amy Park: Well, I mean, urinary incontinence is - go ahead.

Dr. Tanaz Ferzandi: No, I was just going to say, I think that's - again, we have to kind of deal with that clinically because one of the challenges that we have, and we have a lot of data to support this, you know, including the RCTs, is that a lot of

patients self-discontinue a lot of their medications in relation to their urinary incontinence, primarily because of side effect profile.

And so, often what we realize is that the patients drop off, and then they keep kind of repeating the cycle, and then they keep coming back into the clinics, et cetera. And so, I think trying to manage these patients in a more expeditious fashion, it is better to perhaps even try one or two medications, but in general, moving them down the algorithmic pathway sooner than later, because there is a huge burden on the system that - I mean, and I work - part of my time is at a government institution at a county hospital.

And I see patients that are churning and churning and churning, not getting care for weeks, if not months, and sometimes even years, before that, something like Botox is offered them, which we can offer in the clinic. So, I think we just have to kind of look at these guidelines and these algorithms, but then kind of individualize them to the clinical situation that's married in front of us, along with the age of the patient, the ability for them to carry financial burdens, and also logistically, how much time is spent going through these algorithmic processes.

Dr. Meredith Loveless: Thank you very much.

Dr. Amy Park: Yes, I will say that the conservative therapy and behavioral modifications can help, but for those patients with severe symptoms, in my experience, it doesn't really help. So, you know, having to consider place patients on meds that are low likelihood of making a dent is discouraging, but also regarding cost, you know, there's lots of data showing that the anticholinergic refill rate at one year is very low.

The efficacy is also low, and the out-of-pocket cost and overall cost with

Botox is lower overall than using the meds, in particular when you look at the higher-cost meds.

Dr. Tanaz Ferzandi: Yes, and I think to piggyback on to what Amy's saying is that the other thing is that we have other options, the neuromodulators. But when you look at the efficacy of, say, posterior tibial nerve stimulation, which falls into the same tier in the algorithm versus sacral neuromodulation, the cost is astronomically high when you talk about nerve modulation of the sacral version.

And then while the cost to posterior tibial nerve stimulation is far less, the time burden is pretty excessive where patients have to come to the clinic for several weeks at a time and then the efficacy in itself doesn't match that of Botox. So, I think you know we're also here advocating for kind of loosening the reins on some of these tiered algorithms that kind of hold us back from offering what we need for our patient.

Dr. Meredith Loveless: Thank you. And I think we concluded our section just in time. I appreciate your participation.

Dr. Ola Awodele: Thank you very, very much.

Dr. Meredith Loveless: Thank you.

Dr. Ola Awodele: So next we have Dr. Moynihan, laryngeal dystonia, and that will be with Dr. Garrett.

Dr. Eileen Moynihan: Dr. Garrett, what evidence, if any, supports use of (botulism) off-label for laryngeal dystonia?

Dr. Gaelyn Garrett: So botulinum toxin for laryngeal dystonia, which historically has been called spasmodic dystonia as you see in the title, I mean, I think there's more than 30 years' evidence that supports its use and it, you know, I think there are just innumerable references, only a very few that were included in your list.

Dr. Eileen Moynihan: What treatments, if any, would be considered failures prior to using the botulinum toxin injections for spasmodic dystonia?

Dr. Gaelyn Garrett: So, you know, botulinum toxin is really the first line treatment. In general, you know, if you think about what other treatments are available, it's, you know, behavioral modifications with speech therapy, oral medications and potential surgery. And there's no question that botulinum toxin - direct botulinum toxin injections into the affected laryngeal muscles is first line. So I would not consider any other treatment prior.

Dr. Eileen Moynihan: Is there evidence as to whether botulinum toxin should be used to treat abductor laryngeal dystonia in addition to the adductor type?

Dr. Gaelyn Garrett: So, I mean, again, it's just a different muscle group. You know, for the adductor type, it's the thyroarytenoid muscle and lateral cricorytenoid muscle complex. And for abductor, it's the posterior cricorytenoid muscle. And Botox has been shown to be efficacious for both.

The issue with abductor is that the PCA muscles are a little bit tougher to access especially in the office. But I think there's plenty of evidence that supports its use for both types.

Dr. Eileen Moynihan: Does the literature support the use of targeting injections using modalities such as vision and palpation versus electromyographic guidance, nerve stimulation or ultrasound?

Dr. Gaelyn Garrett: So I don't - I'm not aware of any studies that specifically compare the different modalities. I think it's very physician specific. I would say that the majority of physicians who do these injections, which are primarily otolaryngologists, and even within that, laryngologists, I think the majority of us use EMG guidance.

There is a small subset that may use direct - well, indirect vision through flexible transnasolaryngoscopy and some, you know, I'm not even aware specifically of anyone who uses ultrasound or nerve stimulation. You're really just recording.

So it's, you know, these muscles are a little bit tougher to get to than some of the other areas that we've been talking about in this Webinar but I think the physician wants to use the right modality to get them to the right muscle. And I think most of it is just EMG.

Dr. Eileen Moynihan: Thank you. What criteria or scales should be used to measure the outcome such as perceptual voice quality measures, quality of life measures such as the Voice Handicap Index or the voice-related NIA?

Dr. Gaelyn Garrett: Yes. I mean, I think patient-reported outcomes is the standard to evaluate the efficacy and I think it should be physician preference. Some people, you know, typically use the VHI. Some people use the V-RQOL. For me, I think the surrogate for a patient-reported outcome survey is that the patients return for their subsequent injections because, honestly, from a quality of life standpoint, they depend on their voice. And, you know, if it weren't working, they would not come back.

Dr. Eileen Moynihan: Is there any evidence to support any limitations of treatment durations for this condition like if this didn't work you should do something else or...?

Dr. Gaelyn Garrett: So, I mean, I think the - first of all, again, for this disorder, the botulinum toxin injections is primary. You know, beyond that, there are other surgical options that are considered. Very few people get response with the oral medications for this.

I think that the question and the nuances of this treatment approach though is very patient-dependent. And I think some of the questions are going to be related to dose response but, you know, I think, you know, I have patients that I inject with 0.1 units and I have patients that need, you know, greater than 5 units for each injection. And there's really no way to predict where each person is going to fall. And so there is a little bit of trial and error at the beginning. We typically would start with a standard dose and see how they do. You have to weigh the side effect profile versus the improvement profile for each person.

Dr. Eileen Moynihan: Is there evidence to support using different botulinum serotypes interchangeably for this?

Dr. Gaelyn Garrett: So they're - if you look at most of the studies, I mean, the large majority are done with onabotulinum toxin. This is, you know, one where we are using such small units, small amounts of units that, you know, we're not typically concerned about antibody formation. I think some of my colleagues do use a different form of the onabotulinum toxin because of their hospital preferences in purchasing. So I think, you know, sticking with the different forms of onabotulinum toxin is probably the predominant type.

Dr. Eileen Moynihan: Are there contraindications for the use of botulinum toxin in this entity?

Dr. Gaelyn Garrett: Not specifically, no.

Dr. Eileen Moynihan: Are there long-term effects of using it? Let's say if somebody couldn't have a surgical procedure or whatever.

Dr. Gaelyn Garrett: So, I'm sorry, can you be more specific with the surgical procedure?

Dr. Eileen Moynihan: No, I just wanted to know if you had to use it long term, would there be any long-term effect of using it?

Dr. Gaelyn Garrett: No. I've been treating some of the same patients for over 25 years and they still get effects and we're not seeing any dose escalation as well. So we have not been concerned with that.

There are certainly short-term side effects that we see and that's where we have to balance the dose response because again each patient is different and the frequency of injections is different. I think that's one question that - I'm not sure you asked that or I guess it's under number three. I think that the dosing intervals quite frankly need to be looked at as each patient's response because everybody's voice demands are different. Yes, this is a functional type problem and, you know, some people need to come back much more often than every 12 weeks and some don't come back for four to six months. So we - there should not be a prescribed limit to how often or how much we give.

Dr. Eileen Moynihan: Okay. Thank you. I think this concludes this section unless anyone else has questions of Dr. Garrett.

Dr. Ola Awodele: Thanks, Dr. Moynihan. So you will stay on and Dr. Kelly will join you as we discuss the sialorrhea.

Dr. Eileen Moynihan: Hi. Is there evidence regarding the use of botulinum toxin for chronic sialorrhea?

Dr. Kelly Andrzejewski: So this is Dr. Kelly. I would say definitively yes. Injections into the submandibular and parotid glands have definitely across multiple botulinum toxin brands. So it's definitely been shown to be effective in reducing sialorrhea.

Dr. Eileen Moynihan: What treatments, if any, would be considered failures prior to using botulinum toxin injections for this entity?

Dr. Kelly Andrzejewski: Potentially, either the scopolamine patch or glycopyrrolate. However, individuals with Parkinson's disease and hallucinations should not take those medications because they both can cause or worsen hallucinations. So there's certain contraindications to using them that I would go straight - would lead me to go straight to botulinum toxin injections and defer those medication treatments.

Dr. Eileen Moynihan: Is there a dose response relationship for sialorrhea with botulinum toxin?

Dr. Kelly Andrzejewski: Certainly if a patient does not notice as great a response, I have gone up on the dose and they do have a better response of higher doses. I typically start with the FDA-approved dosing recommendation.

Dr. Eileen Moynihan: Okay. Is there any evidence to support any limitations for frequency intervals or treatment durations for this condition?

Dr. Kelly Andrzejewski: In my clinical opinion and experience, the patients continue to receive benefit years after initiating injections. However, some individuals do

notice that injections may wear off before 12 weeks and I've been able to see, like, if the injections wear off at ten weeks just by default injecting patients every ten weeks if insurance approves allows good coverage for treatment without having to necessarily change the type of botulinum toxin brand.

Dr. Eileen Moynihan: What contraindications might there be for the use of botulinum toxin, excuse me?

Dr. Kelly Andrzejewski: If the patient already has excessive dry mouth or in some cases potentially dysphasia.

Dr. Eileen Moynihan: And are there any long-term effects for use of botulinum toxin?

Dr. Kelly Andrzejewski: No, not that I'm aware of.

Dr. Eileen Moynihan: Okay. That concludes this section for me unless anyone else has any questions for Dr. Kelly?

Dr. Ola Awodele: I did have some questions, just a little bit of clarification. (Stephanie), could you go back one slide please?

So when it comes to the dose, like, what we would consider an off-label dose? Is there any literature to support using that, using off-label doses?

Dr. Kelly Andrzejewski: I am not specifically sure on that. I'm not going to make a statement that that is the case. But in my own clinical practice or experience going above initial dosing definitely has benefited the patient.

Dr. Ola Awodele: Okay. Yes, I didn't - I do realize that clinically but I just wanted to see whether...

Dr. Kelly Andrzejewski: Yes.

Dr. Ola Awodele: ...there was - like how would you decide what off-label dose to use? So that's why I was kind of asking if there was any...

Dr. Kelly Andrzejewski: Yes.

Dr. Ola Awodele: ...literature that shows how to kind of step that up or something.

Dr. Kelly Andrzejewski: Yes. No, I mean, I most commonly inject Xeomin and then will increase in increments of 50 units. That's just my own personal experience.

Dr. Ola Awodele: Thank you. Okay. All right, thank you. That's all I wanted to ask just to kind of clarify that portion. Does anybody else have any questions for Dr. Kelly concerning this topic?

No? Okay. We'll go on to the next topic, (Stephanie). Thank you.

Dr. Trimas, that will be you with Dr. Baratta. Dr. Kelly stays on and Dr. Christina Kwasnica. So, Dr. Trimas, are you on?

Dr. Scott Trimas: I am on. I'm ready to...

Dr. Ola Awodele: All right. All right. Thank you. Thank you.

Dr. Scott Trimas: All right. If anybody hears in the background, some screeching it’s the Blue Angels going by and no matter what I do, I can't lessen the noise. Anyhow, so I apologize if you hear that in the background.

Is there any evidence regarding the use of botulinum toxin for spasticity?

Dr. John Baratta:: Hi, this is John Baratta. I'm glad to go first. And maybe we could take turns since there are three of us. Yes, there is good evidence among a number of large trials showing that botulinum toxin is effective for reduction of spasticity in both upper and lower limbs.

Dr. Christina Kwasnica: And this is Tina Kwasnica. I would agree. There's significant evidence of the use of spasticity of cerebral origin, both for upper and lower extremities, with each one of the botulinum toxin preparations.

Dr. Kelly Andrzejewski: And I would confer with them. There's not much to really add to that.

Dr. Scott Trimas: All right. I'll quickly follow up on your question. You said of all the different botulinum toxins, from what I understand, not all of them are approved for those indications, wouldn't that be correct?

Dr. Christina Kwasnica: That is correct. So onabotulinum toxin is approved for upper and lower limb spasticity. Inco is - or abo is approved for upper and lower. Inco is approved for only upper and I think ribo is only approved for upper as well and that's the botulinum toxin B.

Dr. Scott Trimas: Okay. Thank you. I just wanted to clarify that.

What treatments, if any, would be considered failures prior to using botulinum toxin injections?

Dr. Christina Kwasnica: So this is Tina Kwasnica. I feel pretty passionate about this. I think that the literature does not support the need to show a failure of oral

medications prior to instituting botulinum toxin injections. There is specific literature in comparison with tizanidine and the neurotoxins. And then there is really - if you pull apart the data on things such as baclofen and at a lower level diazepam and tizanidine, the literature doesn't support that there has to have been a trial of those prior to undergoing neurotoxin treatment.

Dr. Scott Trimas: Okay, thank you.

All right, the third question I'm going to phrase it a little bit differently and basically when and when is not EMG or nerve stimulation used or necessary for the treatment of spasticity?

Dr. Kelly Andrzejewski: I routinely use EMG guidance when targeting muscles. I think it's important especially if it's specific to certain muscles and it's not just like complete contracture that you're targeting. It just I think provides assistance and good clinical evidence that you've hit the correct muscle target.

Dr. Christina Kwasnica: Yes, I would agree with that. I believe that, you know, the product inserts, all our training tells us that you should use something to localize though it doesn't differentiate between EMG, nerve stimulation and currently ultrasound guidance but does believe that there needs to be something beyond anatomic localization.

It's interesting when you peruse the literature because that's the standard of treatment. To find literature studies in the last 10 to 15 years that even compare anatomic guidance to guided injection is incredibly difficult to find. So it's a standard and really at this point in time is really the question of, is there a difference between the electrical variations, EMG and nerve stimulation versus the ultrasound which is kind of the - I think the next question to be asked for those of us who are injecting for spasticity.

Dr. Scott Trimas: All right. Thank you. What about what objective criteria or scale should be used to measure outcomes, if any?

Dr. John Baratta:: I think monitoring patients' spasticity with a scale such as modified Ashworth is appropriate and I think even providers use that. Some others could assess range of motion, caregiver burden, pain, et cetera, but I think modified Ashworth is the most reasonable in a clinical setting.

Dr. Christina Kwasnica: Yes, I would agree with that. I think in clinical practice, modified Ashworth is kind of the baseline of what we're monitoring. But then beyond that because the functional scales that were used in the different studies allow for a variation in what the functional outcome is for the patient, whether it'd be a patient movement outcome versus caregiver outcome versus pain outcome usually we just use a goal setting and goal attainment scale. So the patient sets the goal prior the physician discusses the goals and then you assess that the follow-up whether that goal was attained or how you may need to change the goal or change the approach to attain the goal.

Dr. Scott Trimas: All right, thank you. All right, next slide please.

Okay. So your typical questions and the first question, are there any - any literature that supports different dosing regimens than recommended by the - or approved by the FDA?

Dr. Christina Kwasnica: I think there's pretty significant literature out there that talks about dosing up to 600 units. You know, I think that there are at least 600 units of onabotulinum toxin. I think that the different studies have, you know, had to - they're often done in the open label extension phase and because of the FDA package insert.

Also, though there is not interchangeability between the different toxins, from a potency point of view, the level at which you can dose abobotulinum toxin is actually got more potency than the onabotulinum toxin, which is - in which kind of goes along with the clinical practice as it is. So I think there's enough literature to support that dose going up to 600 units and I think for those of us who are practicing especially if you're doing two-limb spasticity, that's a pretty typical dose for treatment.

Dr. Scott Trimas: I'm going to piggyback on that question - on that answer that you had there. Using those larger volume of units of Botox, how concerned are you if you say you're treating two limbs at a time or bilateral limbs at a time, you're using a large volume of units, when do you start worrying about things such as systemic toxicity at that point?

Dr. Christina Kwasnica: So in my clinical practice, I usually weigh the risk with regards to patient and the amount of muscles that are being treated that are close to the neck like shoulder girdle muscles as far as whether I have a concern.

Specifically, about weakness leading to dysphasia is the side effect that most concerns me in my population. So I think that being very careful with regards to timing of dosing, making sure somebody doesn't have an intercurrent illness, you know, making sure - I actually think when I'm going at 600 units using the 90 days is the safest route for those patients because you allow a bigger gap between injection that potentially is going to decrease that potential for risk.

And then obviously localization, knowing where you're at and where you're putting that medication and being cautious as far as volume injected as well

because increasing the volume injected can be pretty powerful in concert with the higher dose.

Dr. Scott Trimas: Okay. So that you mentioned though in your clinical practice supporting literature though for using large volumes of Botox, you know, and risks of serious adverse effects.

Dr. Christina Kwasnica: Right. So, you know, there are - and I work in both the pediatric and the adult space. So there are definitely cases of systemic botulism and systemic side effects from the higher doses. Generally more actually discussed in the pediatric realm because the dose per body weight is far higher than the dose per body weight in an adult. So that's where those original cases were - came from.

In the majority of my patients, if we're staying at that, like, 600, the literature both in the practice guideline from AAN, some of the other, like, the - these extension studies that were done, they really show, like, the ASPIRE trial and that they didn't show any difficulty up to that 600 units. The question is beyond that and beyond that is not in large trials. Beyond that is in case series or case reports. Do you get any extra benefit to treating above 600 units or is your risk then, you know, is the risk exceeds your potential benefit?

Dr. Scott Trimas: All right, one last question. Most of these have already been asked. I'm going to deviate a little bit. So you mentioned time interval. So if you're injecting large volumes of - or large amounts units of Botox for treatment of spasticity especially in the limbs, whether it'd be the upper or the lower limbs, you mentioned 90-day intervals between treatments. So is there any guidelines, either societal guidelines or literature, that supports more frequent or less frequent intervals?

Dr. Christina Kwasnica: There are no societal guidelines supporting less frequent intervals. So the practice guidelines that came out of AAN do not support less frequent intervals. There is upcoming guidelines from the AAPM&R that will, I don't believe, support less frequent intervals. I think that we haven't - I'll speak as somebody who's injected for many years and many patients who've been receiving injections for 15, 20 years. We're not seeing immunogenicity in the way that we thought we, you know, we had originally thought we were going to see.

However, I think we still are cautious that we're - that in what we're doing with spasticity we're - we really are injecting at a higher dose than some of the other indications. And so moving the bar closer, unless it's a special situation where your risk outweighs the - or the benefit outweighs the risk that there's not a lot of benefit to making that interval shorter.

Dr. Scott Trimas: All right, that's really the last question I have. Thank you.

Dr. Christina Kwasnica: Okay.

Dr. Ola Awodele: All right, thank you very much. Dr. Trimas, if you could stay on. Dr. Yang was able to join us and we think we appear to have a little bit of time. We want to give her opportunity to kind of answer the questions on facial dystonia. And then after that, I will need Dr. Kettler to also go ahead and ask her the questions.

So, Dr. Yang, if you're on, if you can start by - if you can come off mute and start by introducing yourself, tell us your affiliation and any conflicts of interest, if there are any. Thank you very much for coming.

Dr. Shiayin Yang: Yes. Thanks for having me. So my name is Shiayin Yang. I am an assistant professor of Otolaryngology at Vanderbilt University Medical Center in Nashville Tennessee and I don't have any associated conflicts of interest or no disclosures.

Dr. Scott Trimas: All right. So would you like me to repeat the questions then again or Dr. Yang have access to those slides?

Dr. Shiayin Yang: I do. I do have access to the slides.

Dr. Scott Trimas: All right. If you want comments and you don't necessarily have to because the other experts have also made comments but if you'd like to make any comments to questions will be great. Go right ahead.

Dr. Shiayin Yang: Sure. I guess just in terms of hemifacial spasms, I think there's a decent amount of literature and evidence to suggest that it has significant benefit on patients. The majority of patients I treat have hemifacial spasms, kind of secondary hemifacial spasms, secondary to some type of injury to the facial nerve.

And in terms of prior treatments before, I would say with the kind secondary hemifacial spasm, one of the main things that I recommend treatment is physical therapy typically before Botox therapy but usually in conjunction with botulinum toxin injections.

And I think the only kind of other thing I would ask or add is in terms of objective criteria and scales to measure the benefits and outcomes. I know there's a lot of different scales in terms of measuring how we're grading these patients. I don't think there's been any standardized. I think if you look between different specialties, there's different ways to grade things. So if

you're looking at primary hemifacial spasms, most people may look at the hemifacial spasm grading scale.

But when we're looking at kind of secondary hemifacial spasm or we also call it synkinesis, we have different grading scales to evaluate these patients, both patient-graded measures as well as physician-graded measures. So I think it's important to have some type of patient-related measures to get - it really guides kind of what your outcomes and treatment and how you're going to continue treating these patients because I don't think there are standard doses. I think it's kind of a tailored plan to each patient.

Dr. Scott Trimas: All right. You want to go ahead and pull up the next set of slides?

Dr. Ola Awodele: Oh, Stephanie, the - yes.

Dr. Scott Trimas: Yes.

Dr. Shiayin Yang: So, yes, in terms of the condition for the literature, it's robust literature. I mean, there's been a lot of different studies showing the efficacy of botulinum toxin used in these patients. And the dosing is difficult because there's no label in terms of how much you should dose these patients. So I think it's, again, just starting at a lower, safer doses. There's been different literature published to show kind of starting off doses in certain muscles because essentially you're treating the entire face and ensuring that you're starting at these lower doses will help kind of you escalate and scale treatment from there.

And third, dose response relation, yes. I mean, if you're injecting these patients with higher doses of Botox, you're going to see - it's not necessarily they're going to have a better response. They just may have a different type of

response in terms of the symptoms they're having. And if you over-inject these patients, you may result in weakness that may be weakness in now closing the eye or more trouble with speaking or eating.

And then evidence - in terms of evidence to support limitations for frequency and intervals, I think general duration I treat most of my patients every three months. And I've been treating patients - there have been patients who are getting treatment for 10, 15, 20 years. So I don't think there is a finality to it that there's, you know, you guys have asked previously, is there a safety concern on how long to treat these patients? I think the overwhelming consensus is that it's relatively well tolerated.

Dr. Ola Awodele: Dr. Yang, I just wanted to interject that for those two it's like is there evidence pointing to it? So is there evidence that...

Dr. Shiayin Yang: I don't know of any - in terms of the intervals to treat it? Yes, there is evidence in terms that there's - I believe it ranges between like 70% and 98% effectiveness every 12 weeks.

Dr. Ola Awodele: Okay. And then...

Dr. Shiayin Yang: And some studies cite between three to four months. I don't know of any specific studies that say a specific period of time because essentially you're never going to cure patients with just botulinum toxin. They're going to need this therapy indefinitely.

Dr. Ola Awodele: Okay.

Dr. Scott Trimas: I'll just jump in and say (unintelligible) I mentioned earlier that there are retrospective studies for 10 to 15 years of treatment of patients showing

continued effect, continued efficacy, tolerability and in fact a lower rate of adverse events as time goes on.

Dr. Ola Awodele: Thank you. So, Dr. Yang, we're going to go on to the blepharospasm. And, Dr. Kettler, if you're still on, would you like to take this?

Dr. Bob Kettler: Sure. I guess the first two questions are somewhat related in that, you know, I guess number two, first of all, are there treatments that should be tried prior to providing Botox for blepharospasm?

Dr. Shiayin Yang: In my practice, Botox and, no, I mean, Botox is first-line therapy for it.

Dr. Bob Kettler: Okay. And would you say that's a pretty gentle practice?

Dr. Shiayin Yang: Yes.

Dr. Bob Kettler: Okay. Yes.

((Crosstalk))

Dr. Scott Trimas: If I may, Dr. Kettler, one point I forgot to make earlier on when we discussed this is that I think it's important for the panel and others to keep in mind that botulinum toxin was actually developed in the lab by Alan Scott over 40 years ago specifically because we had to treat blepharospasm was incredibly poor. And so the initial studies leading to the FDA approval of this drug really were centered around the treatment of blepharospasm, hemifacial spasm, paralytic strabismus primarily because there were no other good treatments.

Dr. Shiayin Yang: Yes, I mean, that's an excellent point because essentially that is how Botox was developed and now for blepharospasms and I think it also is a testament to how safe it has, how well-tolerated it's been in these patients.

Dr. Bob Kettler: Okay. All right. And are there objective criteria that can be used to determine treatment effect and also when patients would need a repeat injection?

Dr. Shiayin Yang: So a lot of my practice is driven - again, I use some of the scales like the facial clinimetric scale, the SAQ scale, which may be a little bit different than what an ophthalmologist may use. But a lot of my practice is driven by patient-driven report and improvement. So if they're saying, you know, my eye doesn't feel as tight, there's less blinking, I'm not having as much pain, vision is better, a lot of it is going to be subjective compared to objective.

Dr. Bob Kettler: Okay, thank you.

Dr. Shiayin Yang: But objective, rightfully so would be on physical exam and examining the patient and seeing, you know, how much are they actually spasming, how does the eye look in comparison to the other eye?

Dr. Bob Kettler: Okay. Let's see. Is there a reason to provide injections more often than every three months? I think you mentioned for the issue we just discussed that you typically do three months. How about with blepharospasm?

Dr. Shiayin Yang: Typically what I find is that it's more - I need to increase the dose. If a patient comes to me saying - you know, before that 12-week period saying, "Oh, my dose wore off too quickly," it's more so that I need to increase the dose. So I tend to stick with the 12-week therapy. I do not know of studies looking at shorter ranges of therapy for that. But in my own practice, it's more that the dose needs to be increased rather than decreasing the time interval.

Dr. Bob Kettler: Okay. And is there evidence to support either staying with one preparation for the duration or is there a need to switch amongst the different preparations?

Dr. Shiayin Yang: So people do talk about concern for potential antibodies formation and trying different types of botulinum toxin. Personally, I've had to do it maybe in one or two patients. It's pretty rare in my practice. So I think it is pretty safe to stay with a single neuromodulator therapy.

And if you're seeing after a while, you know, the patients who require an increased amount of dose or they're feeling like it's wearing off sooner, then that could be a consideration for trying a different type of therapy.

Dr. Bob Kettler: Okay. Do you feel there are any contraindications to the use of botulinum toxin injections?

Dr. Shiayin Yang: The only contraindications would be if they have some other type of neuromuscular disorder. If for some reason at the office site there was some type of infection or local, you know, skin reaction around the skin that would be temporary in which you wouldn't want to inject in that area.

Dr. Bob Kettler: Okay. Ola, I'll turn it back to you.

Dr. Ola Awodele: Thank you very much. On behalf of all of us, that is National Government Services, Noridian , Novitas Solutions, First Coast, Wisconsin Physicians Services, Palmetto GBA and CGS, I would like to thank everyone especially the subject matter experts for making this meeting a very robust one and I'm sure we all enjoyed the discussion. So thank you very, very much.

In terms of next steps, I wanted to first of all remind everybody that we usually use evidence about being our guide which I had quoted in the beginning. According to our work instructions, evidence and literature is the main stake of our guide along with guidelines.

So the next thing for us will be to go back, re-listen to this and start our process to develop a draft policy on this.

In a while, the - after this has been transcribed, the recording transcribed, there will be access to both the recording and the transcription on our various Web pages. So just stay tuned and just continue to check and you will be able to see it when it's available.

So in lieu of any other comments by any of my co-CMDs, which does anybody want to have any closing comments that they would like to make?

Okay, hearing none, we'd like to thank everybody and the meeting is officially over. Thank you very much. You may now hang up.

Coordinator: Thank you. This concludes today's conference call. You may go ahead and disconnect at this time.

END