Treatments for Progressive Multiple Sclerosis with Dr. Patricia Coyle

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). It is a leading cause of disability in young adults. For some, MS is a disease with one or two acute neurologic episodes and no further evidence of disease activity. In others, it is a chronic, relapsing, or progressive disease with an unpredictable clinical course that may span 10 to 20 years, during which time neurologic disability accumulates. There are four subtypes of MS, with three of the variants actually being progressive forms. And today as we launch our talk series on Multiple Sclerosis we will be discussing Treatments for Progressive Multiple Sclerosis with our featured expert Dr. Patricia Coyle.

Full Transcript:

Priya Menon : Hello everyone and welcome to the Cure Panel Talk Show. I am Priya Menon, Scientific Media Editor at Cure Panel joining you from India and I welcome all of you this evening to our first discussion on Multiple Sclerosis.

Started in Aug 2012, the Cure Panel Talk show is broadcast live on BlogTalkRadio and brings together experts and patients for a discussion on important topics in healthcare and medical research. The show has hosted eminent physicians and researchers from leading Medical Centers such as Harvard Medical School, Mayo Clinic, MD Anderson, Washington University St. Louis, University College of London Hospitals for discussions on topics ranging from multiple myeloma, prostate cancer, breast cancer to yoga and cancer nutrition. The show has been replayed and heard over 125k times.

And we are excited to launch our talk series on Multiple Sclerosis. Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). It is a leading cause of disability in young adults. For some, MS is a disease with one or two acute neurologic episodes and no further evidence of disease activity. In others, it is a chronic, relapsing, or progressive disease with an unpredictable clinical course that may span 10 to 20 years, during which time neurologic disability accumulates. There are four subtypes of MS, with three of the variants actually being progressive forms. Today as we launch our talk series on Multiple Sclerosis we will be discussing Treatments for Progressive Multiple Sclerosis with our featured expert Dr. Patricia Coyle.

Dr. Coyle, is professor and vice Chair of neurology, and the director of the Multiple Sclerosis Comprehensive Care Center at the Stony Brook University Medical Center, Stony Brook, New York. Dr. Coyle is the author of numerous articles on clinical and basic research aspects of multiple sclerosis (MS) and neurologic infections and she is recognized as a leading expert on MS and neurologic infections. She is currently involved in a number of therapeutic trials testing new immunotherapies for MS. Dr. Coyle, its an honor to have you here with us, welcome to the show.

My co-host for the show today is myeloma survivor and editor of myelomasurvival.com, Gary Petersen. Gary is now 8 years into complete remission post a stem cell transplant. He works with Myeloma specialists to provide life expectancy and survival rate data through his site. Gary has been very gracious and is here to help us host our first show on multiple sclerosis. Welcome, Gary.

On the panel are multiple sclerosis patients and advocates: I welcome:

Bradley Mann – Bradley was diagnosed with multiple sclerosis at the age of 35. Brad and his wife Robynn have recently launched their website sleepingwithms.com and they also blog about life with MS, Narcolepsy and a busy family with four children on Everyday Health.

Kristie Salerno Kent – Author of 'Dreams: My Journey with Multiple Sclerosis," Kristie Salerno Kent was diagnosed with multiple sclerosis in 1999 and since has recorded and produced her debut solo album, "Believe." and produced and directed "The Show Must Go On," a documentary designed to help others understand the physical symptoms associated with MS.

Bonnie Cohen – Bonnie is a licensed physical therapist, specializing in orthopedics. She works with a variety of patients with different injuries of the spine, upper and lower extremities and occasionally sees patients with varying neurological issues at First Rehab in Spotswood.

Towards the end of the discussion, we will be answering questions submitted via mail or posted on our website. If you have a question for our panel, please press1 on your keypads and we can bring you on-air to ask your question.

With that I will hand over to Gary..who will begin with the show…Gary you are on-air!

Gary Petersen : Thank you. Can you hear me well enough Priya. Priya Menon : Yes Gary loud and clear. I am on my cell phone so I apologize for any interruptions in the service beforehand. I would like to thank Priya and all the people from Trialx for providing this forum for people with Multiple Sclerosis, just as she has other forums for breast cancer, multiple myeloma, colon cancer and number of others, because with this we are able to bring to the patient community experts in the field, that in many ways knows, not everything, but so much about these particular diseases specially some that have been so very difficult to treat as is Multiple Sclerosis. I became involved with multiple sclerosis may years ago when I was with, in Texas, San Antonio, Texas, where I actually headed up the Multiple sclerosis walk for a number of years, and so I get to know a number of people, and Understand how terrible this disease can be to those people. Welcome doctor and welcome panelists to the program. Dr. Coyle could you please tell me and describe the difference between the various types of multiple sclerosis and this progressive multiple sclerosis seems to be the one that is far more difficult to treat. What % of the population of the MS patients have this particular disease.

Dr. Patricia Coyle : Well, 85%, 85-90% of MS patients start with the relapsing form of the disease, so that is statistically, the much more common form. Only 10-15% start out with progressive MS from onset. However, the natural history of untreated relapse, and that seems to be transition to progressive disease, and though I can't be absolutely sure about this statement, I think that lasting long enough, you would see the vast majority of relapsing patients untreated move into a progressive state of their disease. If we were defining progressive MS, we are talking about the insidious onset of clinical symptomatology, with gradual clinical worsening, very slowly looking at months at a time, that has to be completely independent of acute attacks relapses, which is the more common form of MS. About 10-15% or MS patients will show gradual worsening from onset. It is very interesting; they tend to have a decade later stage of onset from the more common relapsing form. Progressive MS from onset typically starts in the late 30's early 40's, and it is the only form of MS that shows no female predominance. It is really a roughly equal gender ratio males:females about a 50:50 split. By definition, primary Progressive MS is Progressive from onset and never have an attack or

relapse whereas, there is an unusual form of Progressive from onset, referred to as Progressive relapsing, which can have one or more superimposed attacks. Honestly in my opinion it is a same thing as primary progressive. If you are progressive from onset, then I think that, MOX distinct phenotype. And then the final Progressive form is called Secondary Progressive – Every secondary Progressive patient started out as relapsing MS, but we know that there is risk for every relapsing patient, to at some point, perhaps years into their MS, begin to gradually worsen, and that point when you have defined that, then it would be considered secondary Progressive MS. So there is primary Progressive and Progressive relapsing which is slow worsening from onset and secondary Progressive MS which is something that occurs after the patient has started out as relapsing MS.

Gary Petersen : Ok. Very Very Good explanation. Thank you. What are the current treatments available for progressive MS?

Dr. Patricia Coyle : Well, I am sorry to say that we have no disease modifying therapy that is proven to benefit the truly progressive slow worsening form of MS at this point in time. And that's recognized as a great lack and is the real focus at the current time in therapeutic trials, in trying to document and find in treatments that would help Progressive MS. However, I would make the following points. We increasingly understand the importance of boosting brain and central nervous system reserves, in every body, even healthy individuals, but particularly for those that have a central nervous system disorder like MS. We now know that paying attention to wellness and health maintenance of features is critically important – and I really consider this as a treatment for Progressive MS. And what I am talking about here is – extremely important that things like Vitamin D and Vitamin B be looked at, and currently we think that we would like our MS patients to run a high normal vitamin D level. You want to be your ideal body weight, you don't want to smoke. You don't want to have high salt intake. You want regular exercise, aerobic exercise, three times a week for 30 minutes. That actually improves brain function. It allows the brain to repair better. You need mental stimulation and socialization -These are key features. You want to make sure things like hypertension or being prone to diabetes or hyperlipidemia, these medical things have impact on the brain and the spinal cord, they need to be treated and controlled and aggressively managed and for people that have stress, it is impossible to take away from stress but you want to make it as mild as possible, and you want to try to effectively treat it. I consider that whole health maintenance and wellness approach, a treatment for Progressive MS. And then finally MS has a lot of symptoms, Progressive MS patients in particular have a lot of symptoms, and symptom management is treatment for MS patients, very important. Because it has such as great impact on quality of life and activities of daily living.

Gary Petersen : Thank you doctor. One thing may be I got.. so my first question and may be what I should ask urgently was, could you please explain, to the audience, and I am sure that most people do know, but what I have been long ago, while I was learning about it somebody mentioned to me, its kind of like the nerves have a insulation – almost like a wire, over, you know the insulation on a cup holder, and that some how this insulation, I think it is called myelin or something like that, This insulation somehow degenerates and becomes a short circuit, and that's really what is happening and what causes, and may be that is a..

Dr. Patricia Coyle : That is a piece of it that is a little bit of an old fashioned concept of MS. The first thing that I would say is MS is the major acquired neurologic disease of young adults. Short of trauma it is the major acquired neurologic disease affecting the central nervous system, the brain and spinal cord in young adults. We don't know the cause. There are genetic factors that increase risk or protect against developing MS. There seem to be very important environmental factors that are at play, early in childhood and

adolescence that are critically important in, let's say Segwaying into MS, and then finally the persons own immune system is attacking their own body organ, the central nervous system, the brain and spinal cord. And we know there is inflammation, immune cells that kind of trade in it the brain and spinal cord and they cause damage to the tissue. Think of the CNS as a master computer. So you spoke about the insulating myelin sheet and that is true. MS is a de-myelinating disease, the immune cells of the individual are stripping myelin, but the wires themselves beneath are hit and that is much more important for progressive MS. Because we believe progressive MS is the neurodegenerative phase of MS, meaning it is hitting the wires, the axons, and hitting the nerve cells that sprout those wires. And you can imagine, if you get lesions in various areas occurring in waves, most of the time in untreated MS individuals, depending on where they are hit, you can get a variety of symptoms. SO this is clearly a major neurological disease of young adults.

Gary Petersen : Thank you doctor. Can you speak about some of the therapeutic trials that are currently testing new immunotherapies for MS.

Dr. Patricia Coyle : Absolutely. So, let's talk about trials. First of all the trials that are looking at trying to slow worsening, slow the progression. And there are a number of them, because this has become a major focus, because it is a big lag. The ten disease modifying therapies that we have approved in the US, are all for relapsing forms of MS. And then there are also, in earlier development trials that are looking at repair at fixing damage, at improving re-myelinization or causing repair and fix damage. And that is a whole different vista of treatment. So when we talk about you know current trials, it very exciting. We have some phase 3 trials. Now, when I talk about phase 3 trials, they are big, hundreds, may be a thousand or more individuals that are multi-centered around the globe. Typically those are the trials that you can wind up going to the FDA if they are positive to trying to get approval for the drug. So in the case of primary progressive MS, there is a major phase 3 trial, with the first approved oral agent called Fingolimod for relapsing MS, and they are studying it in whether its been efficient in primary progressive MS. There is also a very interesting major phase 3 trial with a monoclonal against B cells. It is an anti CD20. It is called Ocrelizumab. These two phase 3 trials in primary progressive MS, should be reporting data sometime in 2015 I believe. In secondary progressive MS we have a major phase 3 trial looking at Natalizumab, that is a humanized monoclonal antibody that is given intravenously once a month. That's on the market already for relapsing forms of MS and then testing in secondary progressive MS. There is also another phase trial, major trial for secondary progressive MS, using an oral agent the name is – Siponimod. That is actually a second generation Fingolimod, and that is in a major trial. In addition to these major trials, there a number of other agents that are being tested. A number of oral pills – *Abutelest*, *the Debinone*, Epigallocatechin galactate, Masitinib, Fluoxidine is being tested in progressive MS. Ameloride, Oxcarbazepine, there is a T cell vaccine that is in a fairly big trial in secondary progressive MS. It is a personalized T cell vaccine. There is a stem cell study that is being tested in. It includes progressive MS patients in a monoclonal antibody that can help re-myelinate – that is going into testing. So a lot of studies are going on.

Gary Petersen : Do you think they look Most promising ?

Dr. Patricia Coyle : I think some of them look promising. Now obviously whan we talk about how quickly, would they become available? Number 1 – The study has to be positive. The phase 3 trails that I spoke about first, if you have one of those phase 3 trials positive then I think that drug would go to the FDA pretty quickly., and hopefully it would wind up being approved. One we move down to the other agents that I spoke about, they are not in pahse 3 trials. They are in earlier trials. So we see the, Phase 2 preliminary trial was positive, then it goes onto a major phase 3 trial, that is what you have to bring to governing agent to really get approval. That is the most definitive proof that it really works. So, that would be a little bit more delayed, but I mean there is such an emphasis. And when you look at the amazing advances made in MS in the last

20 years, and now at the current progress in progressive MS, everybody realizing we need to get good treatments for progressive MS, I think it is only a matter of time before we establish therapies for progressive MS.

Gary Petersen : Oh, fantastic doctor, thank you very much. What I will do now is, I will open it up to the panel members. Will take about 15 minutes and go through the questions from the panel members. Each panel member will ask question and then we will go on to the next and so on until we are done with the 15-20 min. then what we will do is go on to the questions fro the audience and then hear from some of our listeners and then go back to the panelist again. So first of all Bradley Mann, are you online?

Bradley Mann : Yes, I am. Thank you Gary Nice to speak with you.

Gary Petersen : very nice to speak with you Bradley would you like to add anything to what Priya had to say about your journey?

Bradley Mann : Sure, absolutely. Actually my phone call is sort of a full circle, for me and that was 10 years ago when I was going through, you know, a time when, uncertainty surrounded my initial diagnosis, you know, the terminology at that time that kept coming up for progressive MS, and I had absolutely no idea – I have heard of MS, but what was progressive MS, I would kind of scary and what not. And I had done some research and I might say it has come full circle, in that at that time, the first book, that I you know really sat down and read, and someone like she into was…..?? Dr. Coyle's book – Meeting the challenges of progressive MS – and I still have that book with all my notes in it. And you know the knowledge I gained from that, and helping to me make the correct decisions down the road. It was very beneficial, so I really want to thank Dr. Coyle, for efforts with that book. And from my wife as well. It was very encouraging. And as far as the question, you know, I find all the current attention being paid now to progressive MS is actually a great welcome. Just for Dr. Coyle, question is that, I am little confused, I guess, why. I guess my initial question is – Is progressive MS separate, could it possibly be a separate disease from relapsing MS in that why is it taking so long to develop, I mean, a disease mapping modifying therapy for progressive MS. Is it just because of the way it is operating or it could be, could it actually be a separate illness in itself and it is that is why it has taken so long?

Dr. Patricia Coyle : Well, I think that is a very good question. I do not believe progressive MS as a separate illness. I view progressive MS as the neurodegenerative component of MS – The injury to axon and neurons. And this is a very important feature about progressive MS, it is age related. It is kind of age locked, where most typically, you see progressive MS, presenting; it is actually in the peri-menopause – for men and women. So it is kind of like midlife, when you typically see it. Now, obviously there are always exceptions, and you can have progressive MS, in much younger individuals, but that is rare. What we now appreciate about MS is that there is injury to axons from the very get go, form the very beginning. Ok. There is neuro-degeneration injury to axons and neurons going on even at the earliest MS time points, but there is no clinical expression of that because there is so much reserve in the central nervous system that can withstand that injury. However, as that neuro-degenerative component is ongoing, at some point ultimately you cross a magical line and the CNS can no longer compensate and now you begin the clinical appearance of gradual worsening. I think that is the best way to think about it. It is very akin to how we understand Alzheimer's and Parkinson's now, where we know that there are the changes ongoing in the brain of Alzheimer's and

Parkinson's years before there is any clinical expression. Because there is such good reserves in the brain that it can bounce back, it can re-circuit things, it can accommodate that injury, up until a certain point. So I really think that progressive MS is inherent in MS and it is the neuro-degenerative phase. Now one might then think about the primary progressive MS patient, which never has relapses, as possibly missing or lacking the local inflammatory phase that is so typical of relapsing MS but, I think, right now, And we think of MS as heterogeneous. I definitely don't think it is a separate disease, but I think it is a separate principal neuropathology.

Bradley Mann : Ok, That is fascinating. If I can just ask a quick follow up. If, primary progressive MS patient would be missing the inflammatory phase or have a very small inflammatory phase, would that then possibly explain why, MRI scans of a primary progressive patient could be quite different than the relapsing patient.

Dr. Patricia Coyle : That is exactly right. Now, I am gonna make a, I thin this is an important point. There is inflammation in all forms of MS including progressive MS, but it is different with relapsing MS. Relapsing MS has focal inflammation and by and large you tend to see more in the way of obvious microscopic lesions on MRI scan with relapsing vs. progressive from onset – primary progressive MS. And primary progressive MS is much less in the way of enhancing, contrast enhancing, gadolinium enhancing lesions, that is much more common in relapsing MS, particularly in early years. However, if you use more sophisticated research or imaging techniques, primary progressive MS has a lot of microscopic injury. It has more microscopic injury than relapsing MS. It is just that the microscopic injury is invisible with regard to how we do clinical MRIs.

Bradley Mann : Excellent. Ok thank you doctor Coyle.

Gary Petersen : yes. Thanks you doctor. Kristie Salerno Kent are you onboard.

Kristie: I am onboard. I just, I wanted to start up by saying that I personally actually currently have relapsing MS, and I think, My hope is that, by sharing a little bit of a background on me, I think Dr. Coyle touched upon it that lifestyle right now, and what I do right now to take care of myself can potentially have possible impact on the course of my disease. Possibly? Is that correct Dr. Coyle.

Dr. Patricia Coyle : In think it is not even a possible, I think is is definitely helping CNS reserve, there is increasing data. So really following a wellness and health maintenance program, I have now come to consider that is form of treatment.

Kristie: Ok, so I was just gonna, just give a little bit of a brief background about myself, I as a child, am a performer and as early as 4 years old, I dreamed of being an actress, a singer, a dancer, a writer director and wonder women, and I just, it was actually once studying musical theater in College, that I started to have issues with my balancing coordination. I kind of felt like certain parts of my body was wrapped in bungee cords and I had very restrictive movements, but I did end up graduating. But a few years after that, while planning my wedding, I started to have physical changes – tingling, pins and needles sensation in my feet and my fingers my feet went numb. My leg, my left leg felt really heavy like I was dragging something along and I kind of brushed of all these symptoms and ultimately woke up one morning, unable to move the lower portion of my body. So, trip to the hospital, and my first MRI and I remember when the neurologist delivered the diagnosis, If I might say, it kind of felt like the curtain on my lifelong dreams was closing and I actually

went through, and I was determine to bear the burden of MS really on my own, so the next few years, I kind of did the only thing that felt natural to me. I pretended, I acted; I hid symptoms like fatigue, and depression and spasms and pain. But the more I pretended, the less I felt like myself, so Once I actually started to go back to the doctor and really talk openly and honestly about the symptoms. I really felt like it was a turning point for me and my ultimate dream above everything else was to be a mom, and I did actually accomplish that dream a few years ago when I gave birth to my son and again, even more recently when I gave birth to my daughter. And there were a lot of things that worried me about having children, and one of them was being able to keep up with them and physically. And I remember there was a family trip to the zoo and I had to keep stopping and sitting down and every step that I took, I felt like I was walking to a bowl of oatmeal. And in earlier years I probably would have denied it or just accepted it, but I think I realized that the denial was just gonna keep me from being the kind of mother that I wanted to be. So it was really turning point for me to address, you know a symptom like walking, which a lot of people take for granted, but it was really impacting my life, and so you know, taking action and fighting back, really is what keeps me moving forward and communicating with my family and my doctor and this awesome MS community, it has really led to independence and a hope that I did not think was possible and I am certainly hearing, some of the things on the horizon makes me feel that much more hopeful. So, that is really the , that is the gist of why I wrote and published the book on my experiences. It was just another way to connect with people on a deep emotional level. And so hopefully, that is a little bit of hope, you know, just like live theater, life is unpredictable, this disease is definitely unpredictable, but I think it is important for people to do exactly what we are doing here today and talk about it, and it is really freeing, I think to share with others, and learn more about their disease and so that is about that all, I want to say.

Gary Petersen : Well, one thing for sure, is that the forums like these which doctors like Dr. Coyle, are so important for the education of you know the newly diagnosed as well as those who are going through the process. So I am certain that there are a lot of people out there like Kristie – I really appreciate that. Do you have a question for the doctor?

Kristie : Oh no I think Bradley really kind of hit mine actually and really also what I asked about, you know, if taking action right now – I think in the beginning I was very.. I would sit back and wait for things to happen and then react, and I think Dr. Coyle has definitely helped me realize in this brief call that it is really important to be proactive and really talk and communicate with our doctors and certainly on symptoms and issues that are impacting our daily living.

Gary Petersen : Ok. Bonnie Cohen are you there?

Bonnie Cohen : Yes I am here, Hello!

Gary Petersen : Hello Bonnie! Did you want to talk a little bit more about your journey and have a question for the doctor.

Bonnie Cohen : I do. First of all Bradley Mann is my patient, and I appreciate him getting me involved me in this discussion. I am honored that he asked me to participate, so thanks Brad. I had a question for the

doctor, first, first of all, Dr. Coyle, Bradley has 142, I was treating Bradley in the summer for few months, for symptoms of balance and coordination issues and I could definitely speak more to that, But this most recent time, he has, he came in with knee problem and I was doing my evaluation and, I found that, his knee was stable to testing, he had seen other doctors, a neurologist I believe, his general practitioner who did testing, they didn't do X- rays or MRIs but did physical testing and found that his knee was stable to testing, and he was sent to me, and I wanted to know – his symptoms are of and on, and initially he hurt himself, he twisted his knee falling over an object at home that he did not see was there, he has visual issues, and so, vision issues, and so he did have a like a mechanical injury but, his symptoms are very severe off and on which is not very typical of an orthopedic problem, and I wanted to know if it is the MS symptoms, maybe, if its the MS that can cause, symptoms in a specific joint to be severe or not severe. Is that an exacerbation of the MS and can it specifically be affecting a single joint on one side. I was wondering if you could speak to that?

Dr. Patricia Coyle : Absolutely. What I am going to say is general comments, because I cant get patient specific without having evaluated spoken to or seen patient. It would be very unusual to have pain localized to a joint in MS. If I see something like that, I really am thinking about a joint issue, and so for example, if you can manipulate the joint and you press in and it hurts, I am not going to blame MS for that. MS is a disease where the pathology is really confined to the brain and the spinal cord, even the peripheral nerves are completely spared. The muscles are really completely spared. Now, Obviously the CNS is the master computer, and it supplies, feelings, sensation and motor control to the whole body, but it would be very atypical to have a localized joint pain and local tenderness. Much more common would be the entire extremity, burning pain, more of what we describe as nerve pain or central pain etc. Obviously, MS is a moving target, and obviously when you have MS, and you may have limitation in your ability to get around. There may be baseline problems with you know co-ordination, weakness, then you are gonna be more vulnerable to have injuries, and obviously just in medicine in general, we are very aware of things like falls etc. So, you can have injuries superimposed on baseline neurological deficits and that is not a very good mix. So you really think very proactively about how to avoid things like falls. Each of my patients, when they have a fall, we go over, was it preventable or not and we try to learn a lesson, because, if they came through without badly injuring themselves, that is great, but we want to learn a lesson so we avoid a fall in future. So, I am thinking that this sounds like that this must be related to the mechanical injury, even though it seems episodic and perhaps that is related to episodic, depending on how that joint is positioned, or stress on it or strain, So I would say, if it is continuing, then may be it needs to be re-looked at from that point of view.

Bonnie Cohen : OK. His complaints were like a squeezing, and the pain was severe. SI the squeezing, kind of, is that more of a neurological.

Dr. Patricia Coyle : It could be but, MS typically does not have a very small area involved, so, typically you don't think like – My big toe hurts- That hardly, that not very not likely to be MS, just because talking about getting a sensory tract, its typically not just gonna affect such a limited area. You would like it to be a larger territory.

[00:36:41] Bonnie Cohen :Ok thank you. I appreciate that.

Gary Petersen : Thank you Bonnie. Guess, we can now go around for a second round of questions, and I will bring it back to Bradley. Bradley do you have another question.

Bradley Mann : Sure. Absolutely. I guess I am……..?? its regarding, MRI SCANS. Now, I guess my bare question is the way of monitoring progress in patients of Progressive MS. And by the way I keep saying the word patients with Progressive MS. I hate using patients, I usually say, someone living with MS and I think, its just, may be I am slightly nervous, that I am saying that. But, for some one living with Progressive MS, for instance relapsing forms of MS, I know that the reliability of MRI is not always the same and what I have been recently, I have seen a WillsEye hospital and including other places do as well, but basically, I have been having OCT scan, and it open up a whole new avenue for my other doctors to monitor my progress, because if that changes the scan over the last two years, and I was wondering, if you envision that in the future OCT scans may be a new lad, just to monitor progress of all types of MS, based on it not being invasive and its low cost.

Dr. Patricia Coyle : Its possible but its clearly not ready for prime time. This is a research tool. So OCT, for the audience is Optical Coherence Tamography, and what it looks at, is the back of the eye, the retina, where you have pure nerves and no myelin at all, and you can actually look at retinal nerve fiber layer thickness. OK. Its a machine, typically, optomologists have it, it is routinely used in cataracts, in glaucoma and other eye disorders, and you can in 5 minutes get a great readout that looks at the back of the retina and measures what would be basically axonal width. So there has been great interest in the MS neurology community about whether this might be an easy way to measure neuro-degeneration in MS, or to track neuro-degeneration in MS. And it is one of the techniques that is being looked at. The problem is that it is clearly not ready fro prime time yet. There are influences of, direct eye injury. It hasn't truly in my opinion yet been mapped out to be representative of more global brain volume loss or brain atrophy. But it may turn out to have a very valuable role. It currently being tracked, and the larger the number of MS patients studies, or MS individual studied that you get, and longitudinal follow up, then I think we will have a much better idea, and we are seeing it increasingly used. I think what Bradley is referring is the fact that in the progressive individual, its very different from the relapsing individual, and so when you are looking at MRI techniques contrast enhancement or T2 lesion per say, may not be the most valuable. Things called T1 black hole are something that can be more helpful, or atrophy measures, that may be whole brain atrophy, that may be segmental gray matter atrophy, or deep gray matter atrophy, may be cortical the more peripheral gray matter. And then techniques that look at microscopic injury, things like mIg transfer imaging, MR spectroscopy, diffusion tensor, imaging functional MRI scans, these are all very doable MRI techniques, but they are really just in research labs right now. They have not come to typical clinical use, but there is a whole, you know, push to really establish progressive biomarkers. And OCT could be one, it could be one, but is not ready for prime time yet.

Bradley Mann : Also would you envision the ability to measure microscopic damage?

Dr. Patricia Coyle : You want to know something, there is a major progressive trial going right now – it is called SPRINT, where they are actually doing it across academic centers in the US. So, its going to be a very interesting experiment, whether using some of these cutting edge techniques at different centers has to be standardized and being read at a central MRI site. So this phase II trial is important, most like a proof of principal study. If this works, and you can do these techniques and standardize them across centers to get uniform ability to read and put that data together, I think that would be a major breakthrough. And this is all potentially you know doable, on regular clinical machines. But I think the first thing you want to show is that you can reproduce results across multiple different machines at different centers.

Bradley Mann : Would that be like standard white board 3.0, that the centers are using?

Dr. Patricia Coyle : So, we talk about like Tesla magnetic strength and probably the most common scans are read like a 1.5 Tesla, but more and more we are getting 3T, 3 Tesla, which is about double the magnet power. And definitely you can enhance the ability to detect small lesions that you get, once its standardized, because, you do need to standardize it and et used to reading it. It is never exactly a piece of cake. You have to work with it a little bit, but it gives a much better pictures. You are right, So a 3T is definitely a better one, particularly if you are doing some of the techniques that are trying to look at microscopic injury than on a 1.5. Yes

Bradley Mann : Ok thank you that will be really exciting, because I have kind of personal experience, My lesion on the MRI is extremely unremarkable as my doctor says, and is completely not consistent with my OCT or my symptoms, though, they have actually, so once those techniques come out, it will be really exciting for myself.

Dr. Patricia Coyle : Its really not that far away. I really see some of these techniques may be used in a new MRI imaging battery for MS occurring within the next couple of years in routine clinical practice.

Bradley Mann : that would be great Thank you.

Gary Petersen : Sure, Kristie did you have a question?

Kristie: Well, I find what Bradley just said so intriguing, because he said his doctor said his MRI readings are presenting unremarkable and yet as somebody, like myself – I consider myself – I mean certainly MS has, as did in the past, has slowed me down quite a bit, but I feel like if the past at least 5 years, I feel like I am very active and yet my MRI presents as somebody who has moderately severe MS, and that I have a extremely high lesion node, I have a number of blackholes and that type of things. So I just found that fascinating, I just found that fascinating, so if Dr. Coyle has anything to say about that, I would be interested.

Dr. Patricia Coyle : Its very interesting. So, exactly, this is a dichotomy, and I think what it boils down to is that, we don't evaluate microscopic injury in MS at all routinely clinically. So what you are seeing, what you are talking about is the macroscopic component, I want to say like the big lesions, the macroscopic component, but then there is a whole microscopic component, and I honestly think that it is probably a major factor in the disconnect. And also just mention that when we do repetitive MRI scans, most commonly it is brain, but the spinal cord is very important and it is only in the last couple of years that we have gotten very good at analyzing spinal cord via MRI scans, and being able to see lesions and areas of abnormality much better. So that is a whole another major part of the CNS that is involved in MS, that get abnormalities, you can get injuries there, and yet we don't use it as much as the brain MRI.

Kristie: And then just a follow up on that, would you say that brain lesions vs. spinal lesions, one has, is

there a prediction in terms of the rate of progression or that type of thing?

Dr. Patricia Coyle : So, it is very interesting – brain lesions and spinal lesions, believe it or not are relatively independent in MS. Spinal cord lesions are one of the features, there is no absolute that is considered, lets say, a check mark for a worse prognosis or would concern an individual. And there are at least some studies that have suggested that spinal cord lesions probably correlate – Well, not lesions so much as may be spinal cord atrophy correlate better with disability than brain atrophy. So there is a little bit of a disconnect that is going on that the imaging level for the brain may not b exactly the same as the spinal cord in MS.

Kristie: Got you.

Gary Petersen : Alright! Bonnie do you have another question?

Bonnie Cohen : I do I do. Dr.Coyle, I know that with MS vision is definitely an issue and it gets progressively worse with the course of the disease. And I know from experience that visison affects balance. And when I do physical therapy exercise with the patient, I work a on coordination balance, if that is what they are coming in and presenting with. What are the long term effects that you have seen, have you seen, has doing the exercises for coordination balance actually pushed off the physical progression that is seen in MS, may be happen later on in life for these patients, because they have relapses. So are they back to square one when they have a relapse or exacerbation, or they better off than they were from the effect of the exercises. I just don't understand it how they would, if they can either push it off to happen later in life, the physical issues?

Dr. Patricia Coyle : So what I would say is as follows – also keep in mind that as we get older. All of our brains are shrinking, so we are loosing abilities from kind of the mid teens early adults on – our brains are shrinking, that is normal phenomenon. So there is an age related phenomenon where the CNS is not gonna work as well. So, have that superimposed on the fact that if somebody has MS and they went untreated there is kind of ad lib hits that are ongoing there. Now, what we are increasingly learning is as follows and this why I made such a major point about it, particularly for progressive MS, because rather than just say, we don't have a disease modifying therapy for progressive MS, the more important concept is we now recognize how important a wellness health maintenance program is to MS. So that can be implemented, I consider that a form of disease modifying therapy. We now know that exercise particularly aerobic exercise on a regular basis affects the brain, affects the brain in everybody, you don't have to have a disease, it affects the brain in everybody. It affects the brain in a very positive way. OK. It really helps promote the ability to with stand insults to repair etc., so to me then it becomes extremely critically important that if you have a CNS disease then following a health wellness maintenance program is even more important for you for that individual than somebody ho doesn't have to deal with issues of having a neurological disease. So the physical therapy is really critically important, and needs to be a lifelong issue, and needs to be maintained and I think that can help the individual cope with the aging process as well as their disease process.

Bonnie Cohen : Ok. Thank you doctor.

Gary Petersen : Thank you very much. We have got about 10 minutes left Priya. So if could have

our listeners who might have a question, hit 1 on their keypad, bring them online. So, please with your questions, we really wait for you to be asking the questions, we do have some here, and so please do hit 1 on your keypad and Priya will bring you online to ask your questions to the doctor.

Priya Menon : Thank You Gary. Listeners can press 1 on their keypads and we can bring you live on air. We have a caller calling from 6069655, please ask your question you are on air.

Caller : Hi that's me, I basically have a question. Ok so I was diagnosed with MS almost a year ago. For years I had symptoms, but they weren't really identified that much – like I had my leg went numb, I had tingly finger set, and I had ….?? protocol things like that, so all this was the all, by the time I got diagnosed, I had optic neuritis. I have also a dozen lesions on my brain. Now I responded well to *Taxidol Tachidol ??, so I* _haven't, I have been having new lesions, but I am just concerned about the initial lesion more. people tell me it doesn't really make a diference in terms of disease progression, but it sounds like it does, because you have that like reserve where you can compensate. I mean what does that mean if you are getting diagnosed lesion if you do have old lesions?

Dr. Patricia Coyle : Right. OK. So, all of those are very good questions, I believe in principle, the earlier the diagnosis is made the better, and if there is an opportunity to go on a disease modifying therapy that can minimize development of new lesions and disease activity, then that is really a good thing. So I think there is a press and urge to diagnose MS early. Ok. Now that having being said, the era of the disease modifying therapies started in the 1990's. For those of us who took care of MS and diagnosed patients, for that and afterwards, there was not a single person who doesn't think we are making a phenomenal difference in changing the natural history of this disease, and making it milder and more controlled. And I think, Ms has been a success story for neurotherapeutics for neurology. So all the natural history studies that added up what is a good prognosis what is a poor prognosis, we are done in the era of no treatment. And if you have a disease modifying therapy for a relapsing form of MS, in my opinion you want to get on it as quickly as possible and also keep in mind that the MRI scan that we typically do that looks at the kind of T2 or flare hyper intense lesion, that has no pathologic specificity. So you could have 2 lesions that appear as white marks on the brain MRI, one could be completely repaired re-myelinated lesion, the other could be a very destructive lesion. They look identical, you can't tell them apart on a typical hyper intense T2 flare study. So there is no pathological specificity. There are other ways like the T1 black hole that we spoke of. That would be like a poor sign to have a lot of T1 blackholes. But I think this is a very optimistic time, and I speak about the DMT's for relapsing MS, we need them for progressive MS. And that is why it is so realized and appreciated and why there is such a major focus. But we also realize and appreciate now, which we did not a couple of years ago, how the key the wellness health maintenance is and I do consider it a form of treatment. And I in my heart truly believe that if we get diagnosed progressive MS patients on sucha program it is benefitting them, it is benefitting the disease, it is keeping them in good shape – as we develop repair strategies and strategies that decrease the neurodegenerative component.

Priya Menon : Thank you doctor. We have another caller on line. Caller calling in from 4145671, you are on air. Please ask your question. Caller calling in from 4145671, if you have a question for Dr. Coyle, please ask your question. I think we should go to the questions that have been submitted. Dr. Coyle we have quite a few questions submitted by our audience, we will quickly go through them. The first one is – is there a relation between MS and lower Vitamin B12 in the body?

Dr. Patricia Coyle : Yes, there is actually. So number 1 vitamin B12 deficiency is a bad thing. It can damage brain tissue and cause dementia. It can damage the optic nerve and cause optic neuropathy. It can damage the spinal cord and cause a sub-acute combined degeneration disease with tract atrophy and can cause peripheral neuropathy. So you don't want to be vitamin B12 deficient. So, it is standard in the differential diagnosis in working up somebody for MS to check vitamin B12. That having been said we know that low normal B12 levels can reflect a relative deficiency in 5% of the 20% of individuals. So, I won't tolerate a B12 level below 400 in my MS patients. Even though it may be normal, if they are below that, I boost them to have a level above 400.

Priya Menon : Thank you, there is a question – What are the contraindications to physical therapy treatment for someone with MS?

[00:56:36] Dr. Patricia Coyle : None.

Bonnie Cohen : Agreed It's all good.

Priya Menon : There are couple of questions on Nutrition. One says – Would switching over to a vegetarian diet help MS patients?

Dr. Patricia Coyle : Not necessarily. The dietary issues are – Number 1 – You want to make sure your vitamin D deficient – which significantly increases your risk for development of MS. they now have recent data that suggest your level of vitamin D is associated with disease activity. So we like to aim for a level of about 70 of vitamin D 25 Hydroxy. You want to make sure your B12 level is above 400. You don't want to be eating a lot of saturated fats, because that is really vascular disease promoting. If you have a healthy balanced diet, may be if you boost unsaturated fatty acids and you watch out for that vitamin deficiencies, then that is a good diet. There is not really documented data for doing esoteric, really difficult diets. At least none have been truly validated to benefit MS.

Priya Menon : Thank you doctor. The next one says – What is the most effective treatment of spasticity in MS?

Dr. Patricia Coyle : So, Spasticity is like every symptom is a multi-factorial issue and so I am not gonna be able to give one thing. If you are spastic, number 1 – you want to make sure you are not constipated; you don't have a cut or an active infection. Because all of those things can make a spasticity worse. Number 2- You should be doing passive stretching, range of motions, on a regular basis, at least for 10 -20 minutes at a time. That is actually a treatment. Stretching and passive range of motion, rehabilitation techniques, and then thirdly, you turn to medications. And the first line medication would probably be considered – Baclofen and Tezanidine – which both work on receptors in the CNS to decrease spasticity, and they work on different receptors, and have different side effects, and so it may be helpful to combine them at lower doses than you would go with anyone alone. And then I think second line would be – Gabapentin and benzodiazepine. And then sometimes you need to do more esoteric such as, selected Botulinum toxin injection, particularly if you have addictive spasm. In some significant spasticity cases, it may pay to have a pump inserted where you

can give Baclofen at much lower doses instilled right into the spinal fluid – a space to hit the lower spinal cord and affect it as positive.

Priya Menon : thank you doctor. I have a question for you doctor Coyle. Actually I was just reading about MS before the show and I came across stem cell therapy for MS. Could you please briefly just touch upon it and some of the clinical trials that are ongoing for this.

Dr. Patricia Coyle : I am sorry, could you please say that again?

Priya Menon : Stem cell therapy. Absolutely. So, I touched on this a little bit before. We are trying to develop treatments that slow down progression in neuro-degeneration. But that doesn't help fix deficits. It does not reverse what has already happened. Stem cells are part of the strategy potentially to reverse fix deficits. Along with others they are not the only one. Their are antibodies that seem to repair or promote re-myelinization, there are also neurotropic factors; there are others agents that can be used to manipulate repair. These are not as far along as the treatments that are aimed at slowing down worsening, but obviously they are very exciting. And keep in mind its not just MS that is driving the CNS repair, such as stem cell strategies, it is Alzheimer's, its Parkinson's disease, its ALS, Its traumatic brain injury, its spinal cord injury, all of those need repair strategies to reverse fix deficits. So, stem cell is one component of that, one domain, and they are all preliminary studies, but we still need to work out what is the best stem cells, what is the best dosing schedule, what is the best amount, what is the best way to deliver it. I think we will se that happening in he next couple of years. I think we will see more and more studies that are helping to define – and I think in the next couple of years, this could very well be a repair strategy, able to be offered to patients.

Gary Petersen : Yes Priya, Dr. I have a question if you don't mind. I am the relapse remitting MS that is 85% of all patients. Would you suggest, you know, is there a certain patient that should be treated and certain patients that shouldn't be treated. OR should all patients be treated, and if so, does it slow the progression. Meaning that they have a good quality of life for a longer period of time.

Dr. Patricia Coyle : Very good question. Very good question, because the major progressive subtype is secondary progressive and that is a relapsing patient. I can tell you my personal belief. I THINK that every relapsing patient should go on a appropriate disease modifying therapy as soon as the diagnosis is made, and I am talking about, ideally within 3 months of the diagnosis being made and ideally within 3 months of the first attack. Now, can that prevent transition to secondary progressive disease, that is a critical feature. The disease modifying therapies we have right now for relapsing forms of MS or anti- inflammatory. But inflammation does produce neuro-degeneration. Particularly early on, there are inflammatory correlates of injury to axons, and we are beginning to get studies that indicate a significant delay in relapsing populations moving into secondary progressive when they are on a treatment, when they are on a disease modifying therapy. We just haven't had them long enough. Remember, the year it was just ushered in 20 – 21 years ago. You need like 30 years to really get an idea on truly changing the natural history, but all the evidence is pointing in the direction that the disease modifying therapy seem to be delaying and hopefully preventing a relapsing patient moving into a secondary progressive phase of the disease. So I am a big proponent of early effective treatment. We have multiple choices now. There are whole different profiles getting on treatment as early as possible. There is benign relapsing MS, but unfortunately its a retrospective determination looking back 30 years, and in my opinion no one has really defined it, it makes up only 5% of

MS. So, if you are betting, you are the one in 20, those aren't good odds, much better to get on a disease modifying therapy in my opinion.

Gary Petersen : would there be any reason not to if some people have side effects that are compromising?

Dr. Patricia Coyle : The point is, you have so many options now that if you have side effects to one, it is highly unlikely you are gonna be sensitive to all of them. So, there should be virtually no reason not to get on a disease modifying therapy.

Gary Petersen : Ok well thank you very doctor. I think you have been very helpful to a lot of people and I am very glad that people and trialx has put this program together and I have an opportunity to have some small part in this initial program. Priya?

Priya Menon : Thank you Gary. Dr. Coyle, thank you very much for joining us today. It has been an honor and pleasure listening to you, and I am sure our audience have benefitted a lot. I thank the panel and Gary for their participation. You can always email me, priya@trialx.com with your feedbacks and suggestions on MS topics that you would like to hear on the show. The link for today's broadcast will be sent via email to all participants.

Please join us again on Monday for our monthly myeloma support group meeting where we are talking with Jim and Kathleen Bond about their myeloma journey. Please visit curepanel.carefeed.net for details of our upcoming shows.

Thank you!