msaa Improving Lives Today!™

Multiple Sclerosis Association of America

Webinar Transcript

Program Title: **"Best Practices in MS: What We Know, What We Don't Know, and What We Hope"**

Recorded On: **September 9, 2020**

Presenters: **Barry Hendin, MD**

MSAA Host: **Gina Murdoch, President and CEO**

Gina Murdoch: Hello and welcome to the Multiple Sclerosis Association of America's live webinar, Best Practices in MS - What We Know, What We Don't Know, and What We Hope. I am Gina Murdoch, president and CEO for the Multiple Sclerosis Association of America and your host for tonight's program.

On behalf of MSAA and our presenter, we greatly appreciate the opportunity to keep you updated on this very important topic. And please know, we hope you and your family are staying safe and healthy in these uncertain times.

MSAA is an extremely honored to host this educational program with Dr. Barry Hendin, MSAA's chief medical officer, the director of the Multiple Sclerosis Clinic at Banner University Medical School, and clinical professor of neurology at the University of Arizona Medical School.

Before we begin, I want to take this opportunity to thank Novartis for making this webinar possible. As you may know, MSAA is a national nonprofit organization dedicated to improving lives today for the MS community. In fact, this year marks MSAA's 50th anniversary as an MS advocacy organization.

Some of our free services include a national helpline, equipment and cooling products, MRI funding, an online community, webinars, and many more free programs available to people living with MS all across the country. Please visit our

website to experience our new COVID-19 and MS (fact finder) tool, which provides ongoing updates and resources on the coronavirus.

Also, please know MSAA has expanded our helpline hours to 8:00 p.m. Eastern between Monday and Thursday. To learn more about these and all the ways MSAA improves lives today, please visit MyMSAA.org or call 1-800-532-7667.

And lastly, please note tonight's program will be archived to our website very soon. For our Q&A session, please type your questions into the chat box and we'll address them at the end of the presentation. Also, if you are having any technical issues, please type those concerns into the chat box as well.

We are so pleased to have you join us for this timely conversation and I am honored to introduce Dr. Barry Hendin. Dr. Hendin?

Dr. Barry Hendin: Gina, thank you very much. I'm very pleased to be able to speak with such a broad audience of people with MS and people who presumably are supportive of people with MS.

When we try to figure out what we wanted to talk about today, the format we chose was one of trying to present what we really have learned about MS over the years that is science based and really beyond opinion.

And then after that, those things we're still trying to work out and are still a matter of opinion and in terms of clinicians you'll see a lot of variation in how we interpret and do the things we do. I wanted to at least touch on those various interpretations that you will be hearing from neurologist to neurologist to -- who focus on MS. And then where we hope for going, where we want -- our understanding and our ability to treat MS where we really are aspiring, what we want this to become ultimately.

So, that's the kind of the three prongs that we'll be doing. And then I hope that I don't speak too very long so that some of the questions, which you all have put in an advanced, Gina has formatted and to have her tee up those questions to me because they are actually excellent questions and focus on the sorts of things that I think we believe our are the subjects that we ought to be talking about anyway.

So, with that in mind, again, I am really honored to be presenting for MSAA -- an organization that I think you know has been one that has been so important in

supporting education in MS, day-to-day needs of people with MS. And for me, it's -- to be able to walk along with them and serve, MSAA has been a real blessing, a real honor.

So, what do we know? Well, I want to bring us back to the early days of MS. And certainly, I was practicing before the 1990s. But until 1993, there were no therapies that were disease modifying therapies. The first disease modifying therapy was in 1993.

So, before that, neurologist would diagnose still with a reasonable degree of accuracy. We could treat some of the symptoms of MS. We could treat relapses, but we couldn't change the trajectory of MS. We couldn't say to someone, we are going to reduce the likelihood of disability. We're going to improve the probability that you will have a life of greater function and greater quality of life.

As of 1993, we got our first disease modifying therapy. I think it is important to recognize we now have over 20. But then there was the first only one, Betaseron. Then there was Avonex, another interferon. Then there was Copaxone, copolymer. And then came an additional interferons and oral agents. And -- but we didn't have enough experience to be able to answer the first question, which was: When should you start the therapy?

You all who are listening, they say, but it is obvious, you start the therapy when a diagnosis is made. But in 1993, that wasn't obvious and there were varying opinions, a very conservative view and that was led by the Mayo Clinic was that MS was a long-term illness, a long-term disorder, a long-term issue. And therefore, you shouldn't begin therapies necessarily early, but you should observe for some time to decide whether or not you needed to jump in with the therapy.

Another group -- and I have to admit I was a latter group -- believed that we should jump in early and treat when we make the diagnosis if at all possible. But it was still debate and I want to bring out that it wasn't -- it wasn't yet. It was opinion rather than the clear information.

The difference was we had data. So, a number of trials were develop around what we called CIS, clinically isolated syndrome, of people who had one event, maybe

optic neuritis, maybe partial transverse myelitis, maybe a brainstem cerebellar problem like incoordination, double vision.

And studies were done with the available agents to say, if you treat people with their first event of CIS, the first relapse, before they become multiple, multiple sclerosis, could you prevent the second relapse in the diagnosis of MS? And the answer was, in those studies, two things evolved. One, those early agents compared to placebo did reduce the likelihood of a second relapse and the likelihood, therefore, of being diagnosed with clinically definite MS.

But the second one was an equally important finding and that was that the people who were in the placebo group who were then transferred to the treatment group two years later never caught up. They always lagged behind in terms of disability.

So, the answer became a solved or a clear-cut answer. If you delay therapy, you ran the risk of creating disability that you would not be able to undo and that people who were treated early really did benefit more. The people who are treated later never caught up. The answer was, you treat as early as practical for the diagnosis of MS. So, we know that, I would suggest.

The second thing we know is the importance of paying attention not just to MS but MS on therapy. So, if you start a therapy for MS, be that an oral therapy or injectable therapy or an infusion therapy, it's important to monitor for two reasons, maybe three. One is monitoring for safety. Is the agent I'm using, which I am hoping will be of more benefit than risk, causing safety problems in this one person?

We know that a population based on the trials that were done, the things that people might experience, we know what might be experienced with each of the of the agents based on the research or the trials that we call Phase 3 trials that was presented to the FDA.

So, one of the reasons we follow is safety. Is there a change in the various components of the blood count? Are there changes in liver function or kidney function? Is there an increase in infection or infection risk, including issues such as PML?

So, on one hand, you're monitoring blood work for safety, you're monitoring MRI for safety, but you are also measuring it or monitoring to see whether the agent you are

using is doing what it is supposed to be doing. We -- in the early days, there was a debate about whether we should call -- if a person was on an agent and they had a relapse, whether we should call that a failed therapy.

And we decided that that was actually the wrong term, that we use the term optimal and suboptimal. For example, if you started some on an agent they broke through, how did you know they wouldn't have broken through more often if they weren't taking the agent? How do you know that they wouldn't have broken through despite the agent?

And so, really it is about whether or not the agent you're using is doing what you wanted to do. All of these agents are anti-inflammatory agents. All the disease modifying therapies are what we would call anti-inflammatory. They're supposed to reduce inflammation. And our marker of inflammation, the one we use the most, the clinical one is relapse. The non-clinical one is MRI.

So, if we start someone on therapy and the therapy has had time to work, will tend to get an MRI. People do it at varying times. Three months to six months is generally what we would choose after starting a new therapy, depending upon how quickly the therapy worked. And then we'll look to see whether or not we have accomplished our goal of reducing the inflammation.

If there is new activity that is currently very active at six months -- we call the gadolinium enhancing lesions -- we know that despite our agent -- six months later, when our agents by and large should be working, that there still inflammatory activity going on, and we would say it is not achieving. This agent is not achieving what I hoped for and that is that I would achieve a sufficient anti-inflammatory response, that I would not see inflammation.

If a person is having a relapse, we would say this is suboptimal therapy. You wouldn't say that a day or two or a week or two after starting a therapy because it has not had time to work. So, what I'm suggesting is that you're monitoring for safety, blood work and MRI. You're monitoring for the success in achieving the goal you set before you. And then you're monitoring by asking the questions about tolerability, is this -- is this agent that you're actually taking without really interfering with your quality of life. That's clinical monitoring.

So, I would say that it is very clear that people on MS therapy need monitoring. The type of monitoring varies with the agents. We have agents that -- one agent that does not require blood work, but still required periodic MRI. Another agent on the other end of the spectrum that requires blood work monthly for four years after you've gotten your last dosage. So, the monitoring requirements aren't identical for each of the agent. But the fact that you need to monitor is in fact a given, for safety and for efficacy, safety and effectiveness.

The next thing I think we know for sure is that the disease-modifying therapies are not sufficient in and of themselves, that there are other issues that create well-being in people with MS. There are other issues that we know lead to worsening outcomes that have nothing to do with taking your medicine or not taking your medicine, which is a given. So, it's a given that you take the medication your prescribed if it is working and if you can tolerate it, that no agent works less well than the one you don't take.

The second part of this though is the need to continue on wellness and the general overview of health. So, we know that smoking leads to poor outcomes in people with MS. If you got MS and you're smoking, you're doing something that is in fact counterproductive. You are taking your disease modifying therapy and simultaneously doing something which is working against disease modification. We just believe that one of the most fundamental things you can do is stop smoking.

Second, exercise. We believe that exercise promotes general health and also improves function and outcomes in MS that people with MS who exercise do better in terms of disability than people who do not exercise. We believe that a healthy diet and maintenance of a good body weight becomes an important part of outcome. And we know, for example, that obesity is associated not just with poor health in general but more disability in MS.

And so, what I'm focusing on here is that the disease modifying therapies are the important base, but there are insufficient without a comprehensive disease management. And that means diet, exercise. That means stopping smoking, taking vitamin D. That means managing symptoms to improve quality of life. That means managing what we call comorbidities and that means diabetes and heart disease, et cetera. Not managing those other medical conditions leads to worse outcomes in MS.

So, as a given, what we know -- what we know is that disease modifying therapies are essential and insufficient in and of themselves, that we have to take care of the whole person. That means how they eat, how they exercise, how their general health is, how they stopped smoking, and their mental health, and that is watching for depression, watching for anxiety, treating those, managing symptoms, managing bladder, et cetera. Again, a given.

I think it is increasingly part of our understanding about when we should not just start therapy but when we should consider changing a therapy. And so, I alluded to the fact that if you run a therapy that isn't working, not doing what you wanted to do in terms of stopping the inflammation, that it is a time to talk with your clinician about am I on the right medicine or do I need something more effective.

If you are taking a medication -- and that means by -- both by MRI metrics and by clinical metrics. If you are breaking through clinically, you are not achieving optimal therapy. If you are breaking through with new MRI lesion, you're not on the optimal anti-inflammatory strategy. So, that's one part.

The second part is, are you tolerating the medicine? I tell people periodically that when I started disease modifying therapy I am saying you will thank me in 20 years and I also say you won't thank me in 20 years if you are miserable every day of the next 20 years. So, whatever I start them on has to be something that is tolerable. There are people who take medications like a good soldier but they're having a very hard time tolerating. We should be able to do better and you should ask us to do better.

They may have stopped her medicine because they couldn't tolerate it. That's part of the conversation. We should do better. You should expect us to do better. You should ask us to do better. So, if you can't tolerate medicine and are not taking it, ask us to do better. If you can take your medications -- if you can't tolerate your medication and are still taking it, talk to us about change.

And then the last time -- the last thing for change is if we're creating hazard, if the medicines we're using are creating dangers, that they are creating liver damage or changes in blood work that is not healthy, changes in (really) the general health of an individual. So, it should be -- it should not reduce health. It should not reduce quality

of life. And it should work. And if it isn't, we got enough therapies right now that we would be talking about change.

What don't we know? Those of you who are listening, if I could poll you, we would hear that some of you are on injectable agents, some of you are on oral agents, some of you are on infusible agents. I would venture without having the ability to poll you that you are on multiple different agents, which means that there is no consensus about which one agent is the right agent for you, which one agent is the right agent for populations. It's lucky, therefore, that we got so many agents to think about.

I have, in the past, compared myself to a shoe salesman and said that my job is to find the right shoe for the right foot, the right therapy for the for the unique person in front of me. And that means a discussion about not just what I think is the right therapy but a discussion about what the person in front of me would like to take, their fears, their goals. So, it is a collaborative process. One size does not fit all.

But the question is, is there an evolution in our philosophy of treatment? And I would suggest that there is an evolution that we know that the injectable therapies while having of the high safety record had a lower record in terms of power for reducing inflammation and that there has been an evolution toward higher efficacy agents, whether that means the oral agents, the infusible agents, or I would say now the new injectable agent, which has -- which has also high efficacy agent, one that was just approved in the recent weeks.

So, the platform agents still are used but a tendency to move toward higher efficacy agent, often those which have evolved after the first -- the first platform agents. So, if you said to me, do I believe there is data to suggest that there is a benefit in the higher efficacy agent for most people, the answer is yes. Is it opinion and still a part of the discussion that goes on across the country? Yes.

Despite the fact I might believe that, do I start all patients on high efficacy agents? The answer is no. After discussions, my practice is to try to take into account the opinions of the people I see and also there their unique clinical profile, which leads us to the next bullet point and that is do we treat to the presumed prognosis. That said, to the presumed diagnosis. It should say, should we treat to presumed prognosis.

We have some indicators, imperfect, as to people who are likely to have a milder course of MS and people who are likely to have a more serious course of MS with more hazard. Our predictive indicators are imperfect and because they are imperfect we can't say can tell from your presentation that you will do well or won't do well. We have some indicators that tend to lead us in the direction.

I would say that most neurologists tend to treat more aggressively with higher efficacy agents if they think the prognosis is worse. And some use milder agents if they think the prognosis is better. I would say that based on studies that have been done in recent years using higher efficacy agents when compared to lower efficacy agents has the same kind of outcome that I told you about the original trial.

Some of the newer trials have compared higher efficacy agents with what we would have called the platform or lower efficacy agents, both reduced. They're called active comparator rather than placebo comparators.

And what they tended to show is, again, they both work. But the higher efficacy agents worked better over the two-year period of the trial and that when looked at in terms of long-term extension -- observation of that population, once they're switched over all to higher efficacy, the groups that were treated with lower efficacy agents don't catch up. So, again, I'm not solved, but with a tendency, I think, in the MS focused community to use more effective agents earlier than had been the pattern earlier.

When to stop therapy? We know that MS becomes less inflammatory as people age. So, the immune system -- there is something called immunosenescence. Immunosenescence means that your immune system is less and less powerful as you age. For MS, it is a helpful thing in that the autoimmune system is less and less powerful as you -- the autoimmune system is less and less powerful as you age too.

People after their 50s and 60s and 70s are less likely to have relapses, less likely to inflammation. And one of the debates right now is, should we de-escalate, and therefore, use a less potent agent as people age? Maybe. Should we stop therapies in some people as they age? Maybe. Do we have the evidence to show -- to show that definitively? Not yet.

There is a study going on at the University of Colorado. The head of that study is Professor Corboy. He is looking at people age 55 to 65 with free of relapses for MRI activity for a period of years and half of them remaining on therapy and half of them are stopping for him to answer the question, are we doing enough good to balance the harm in the therapies as people reach certain ages?

It still won't -- we'll know about population. We'll know about what agents tend to be the least risk for relapses and the most need, therefore, for ongoing or the least need for ongoing therapy. But the individual in front of me will always be unique, and I'll have to answer that question always. Yes, you're 50. What should we do about you? You're 60, what should we do about you? You're 70, what about you? Populations will know individual agents -- I'm sorry -- individual people still as always. It's an ongoing discussion.

So, what do we hope for, for the future? We hope that we'll be using something besides MRI as biomarkers to tell us about prognosis. One of the indicators for prognosis that we -- that I talked about was the MRI, but were looking for inexpensive blood tests that may tell us something about whether a person is highly having a lot of inflammation or low levels inflammation. The prime candidate now is called neurofilament light.

Neurofilament light is a breakdown product of the neuron -- of the skeleton of the of the neuron. And when a neuron dies, it's released into the spinal fluid and then into the blood. We got now very sophisticated test to see how what the level is in the blood in order to determine the level of inflammation that may help us determine prognosis in an individual. Do you need a high efficacy agent? Might you get by with a lesser agent? We're looking at other markers as well that deal with the glia and the astrocytes to tell us about prognosis. But they would also be helpful in telling us about whether or not a particular therapy is working.

People will often say to me how do I know if my therapy is working, and I tend to say, is your MRI OK? Are you feeling OK? And if you have relapses and you're stable, it is working. But the other way of looking is to look to see whether there is a breakdown in the neuron. So, if we see a -- if we have -- if we have markers like neurofilament light that show a high level of breakdown despite a therapy, it may be a reason for us to say, ah, this is not doing the work we wanted to do that and not just requiring MRI.

The future, we're hoping -- we have reached a level where we have been really good at reducing inflammation and attacks. We're still working on progression. We hope to do better with progression. And this says, in the future, we're hoping that we'll also be able to repair injured neurons and allow for remyelination.

There's work going on and some the questions which we posed to us today by you all were the question about what's the state of the research in remyelination, what's the state of research in terms of repair. I'll be happy to talk about that when Gina tees up questions for me. But I think we are not yet there at a level that we can constantly tell someone that we are repairing and remyelinating the central nervous system. But we really have made great strides.

And then in the end, we still need to understand what are the variables that cause MS. We know that there is an inherent vulnerability and some genetically based in terms of how many genes are protective versus how many genes are susceptibility genes. So, we know a bit about the genetic susceptibilities.

We know that they are not determinants in terms of -- your genes will not tell the whole story. There has to be triggers that are going in the environment whether it's EB virus, whether it's cigarette smoking, the lack of vitamin D, et cetera, et cetera. Those are the things that are triggers.

And so, what's the cause? We know some of the genetics, but not enough. We know some of the triggers, but not enough. We really are looking for the time when we can say, we understand the cause of MS sufficiently and the trigger sufficiently that we can cure or end MS, and that's ultimately the goal for all of us, the end goal.

So, those are things I wanted to say. Those are the things that -- are the questions I ask myself virtually every day. I would now like to be quiet in remaining, I think, 25 minutes or so and answer the questions which you posed advanced or which are on the question block.

Gina, your thoughts?

Gina Murdoch: Wonderful. Well, thank you so much, Dr. Hendin. We really appreciate your perspectives, your compassion, and spending your time with us. So, I wanted to go

to some of the questions that we have. We have some questions sent in advance and some that have come in the chat box.

So, one of the first ones that we had and there was a number of people that asked this talking about, can you explain a little bit more about secondary progressive MS and what's the difference is between active and inactive secondary progressive MS, and whether relapsing-remitting treatments should ever be considered for secondary progressive MS?

Barry Hendin: Sure. So, the first thing is definitional and that is what is progression and how do you differentiate the forms of progression? A lot of work was done by Dr. Fred Lublin in Mount Sinai in New York in trying to really define these terms for us.

And so, with the tip of my hat to Dr. Lublin, to Fred, we would say this, that there is a group of people who never really experienced significant relapse pattern that they don't have an onset with optic neuritis or spinal cord injury or brainstem injury as the people's relapsing MS do but rather have a very slow, insidious onset. That's primary progressive MS, MS without a relapsing history. That's 10% or 15% of MS.

The 85% of MS is the relapsing form of MS. A number of people who have relapsing MS will go on late to what is called secondary progression. So, the typical is for the early years of relapsing MS to be punctuated more by the inflammation, relapses with improvement or even return to baseline after an attack. And then if there is a failure to return to baseline, at least the stability after that.

There is a phase later in MS where despite the lack of relapses, people tend to say, I'm not as good as I was last year, my legs are weaker, my coordination not as good, et cetera, et cetera, et cetera. That worsening independent of relapses in people who had relapsing disease begin with. Is what we call secondary progressive MS.

For me, the most hopeful part of the whole issue of secondary progression is the amount of attention we're now paying to it. So, I want to turn back the clock in a couple of ways. One is, again, when I was a young neurologist, we couldn't relapsing MS. We didn't have any disease-modifying therapies. And neurologists were known for being nihilistic and that is, they would say we really can't do anything. It wasn't true because they could still deal with the symptoms of MS. But there was a lot of -- lack of appropriate energy and focus. That changed after 1993.

There was a lot of early literature that said, if a person becomes -- starts to show disability, walking problems, for example, that at that point in time there wasn't much that we could do. So, 20 years ago, even after the disease modifying therapies came out, there was a nihilism about progression that once you saw significant progression that was really all you could do.

One of the things that we have been seeing -- and I would say that the trials of one of the agents -- in this case, siponimod, which was for secondary progressive MS, showed us that there was the ability to treat people with a high level of disability up to EDSS scores of 3.5, 4.5, 5.5, 6.5 and that we could, in fact, produce a better outcome, less disability progression in people who already had substantial disability.

So, my view is that the recent studies have been powerful at telling us, don't give up. There is more we can do. What the FDA said was there are two phases of secondary progression. One is the phase where there are still relapses despite progression or there are still new MRI activity despite progression or at least activity within the last -- within the previous two years. And that's what the FDA is calling active secondary progression.

So, virtually, all the agents we are now seeing. So, virtually every agent -- and I have to hesitate to think that there is one that doesn't not have it will say that it is approved for relapsing forms of MS, including in some cases, CIS, in all cases relapsing MS, and what they are calling active secondary, which I just defined it, as secondary with some level of activity during the past couple of years to mean relapse per MRI.

We've shown we can make a difference with our agents and that means with the agents that are commonly used, for me, it is something that us remain optimistic when there is progression, particularly when there is active progression. There is more we can do with our disease modifying therapies to change outcome.

We've seen less and less disability in the current era than 20 years ago, 30 years ago, and that's because of the agents we're using and because of the increased effectiveness of the agents were using. A long answer, but it is about this. Active secondary progression is when you have had a progressive phase but still if in the past two years some form of activity, MRI or clinical.

The most important messages is, it's still a time when we need to pay attention when our agents still work and we ought to be very attentive. The biggest game for me is that sense of optimism about what I can accomplish in that state, which wasn't so clear years earlier. Thank you, Gina.

Gina Murdoch: Thank you, Dr. Hendin. Our next question and it's a timely question, talking about what your thoughts of someone living with MS and COVID-19 vaccine, especially in the halting of the AstraZeneca trial, just kind of what your thoughts are on that subject.

Barry Hendin: So, the things that -- the first thing I -- sometimes I find myself quoting Bob Dylan in the line from the song, The Times are Changing, which is: Don't speak to you soon. The wheel is still in spin. The losers now maybe later to win, and the times are changing.

So, the virus has been with us for the last 10 months and we don't yet know enough, but we are evolving better and better understanding. The givens that we now say are the following. We do know some things -- again, if you go to what we know or what we don't know, we know that you reduce the likelihood of catching it if you wash your hands, if you wear a mask in public places, if you practice a sensible social distancing, that those remain sensible ways to reduce the likelihood of getting COVID-19.

It looks like the people with MS are no more likely to get COVID-19 than the general population with the same levels of ability and comorbidity. It looks like the people to greatest risk are the greatest risk because of their age, the older you get, the greater the risk, and their comorbidities - smoking, kidney problems, obesity, high level of disability, and untreated diabetes, untreated heart disease, untreated lung disease. So, the big driver does not appear to be MS, but level of disability does play in and comorbidities and age play in even greater.

With respect to the disease modifying therapies, although the original worry was that one particular therapy might be better or worse than another, the tendency for us now is to say that MS is the greater known risk and that we would not have a person stopped their therapy nor change their therapy. So, don't stop your therapy or change therapy certainly without talking to your clinician.

The data we have so far, including the data from Washington University, Dr. Anne Cross, (COViMS), her survey of the American scene looks like the risks are not excessive with the agents that we're using and that the we tend to keep people on their agent.

With respect to vaccination, we don't yet know what the vaccination will look like. We don't -- we think it will be a non-live virus, but we do not know that. We think that it will provide a degree of immunity, but we don't know how perfect that degree will be. We don't know how long-lasting it will be. These are questions to be answered.

The AstraZeneca pause because apparently -- and I don't have all the information on this -- a person developed transverse myelitis, a serious repercussions, a serious sequela of the therapy. So, it tells us that it is appropriate for all the makers of the vaccinations to continue to do what they're doing, and that is proper Phase 3 trials with placebo control to see whether it is safe and effective.

And I believe that by the first of the coming year we will likely see a non-live virus, which is partially effective or substantially effective in a -- in a number -- in much of the population. And if the question is, will I be willing to stand in line for it, the answer is yes.

Will our MS therapies in some way mute the response to those vaccinations? Number one, you can't tell for sure without knowing what your vaccination is. But some of the B-cell depleting therapies may mute or reduce the immune response. But we'll find it out with time. A long answer, most we're still waiting to know.

Gina Murdoch: Wonderful. Thank you so much. So, if we could circle back, there were a number of questions about remyelination and where we are in that research. So, if you could address that.

Barry Hendin: Sure. And I have done -- I participated in some of the remyelination trials. But let me tell you, we know that people with MS after an episode of demyelination tried to remyelinate and that their ability to remyelinate is diminished compared to the general population. The older you get, the less and less effective it is.

There is a gene that reduces the remyelination, called the LINGO. So, the first attempt to try to remyelinate was to block the gene that blocked remyelination. The trial has mixed results and I was in that trial, but it is still ongoing and that is -- is there

a way to create remyelination through blocking the gene that prevents it. Again, work in progress.

Work out of the University of San Francisco is looking at a wide variety of commonly used therapies, including clemastine, an antihistamine, which looks like it has at least some ability to promote remyelination, a work in progress.

Some of the work right now is really looking at the cells that create myelin, the oligodendrocytes. They are precursor cells. And so, some of the work is, can we find the ability to (regrow) the precursor cells, direct them to where they need to be, and then turn them on. So there a lot of different strategies and the -- hold on just a second, my computer wanted -- good -- so, there a lot of strategies right now. And the question really is, which strategy is going to be the successful one. I believe we will ultimately have a successful strategy. It won't be tomorrow. Gina?

Gina Murdoch: OK. Thank you very much. Yes, I'm sorry. There were a number of questions addressing fatigue. And one says, I always hear that exercise is good for MS, but my fatigue makes it difficult to move sometimes. Is there any advice you can offer about overcoming this obstacle?

Barry Hendin: Sure. And I'm going to talk about fatigue. Again, as you noticed, I will give you long answers for short questions. But my answer here is everybody, I think, knows that the most common symptom of MS is fatigue. Fatigue is not unique to MS. And people who don't have MS also experience fatigue, but generally for reasons they understand. They will say, I didn't sleep well last night. I pushed too hard at an activity or was too stressed or something else that that is -- that will explain it.

The problem with MS fatigue often is that it is there independent of the things you are doing, your sleep or your physical activity, et cetera. So, the first thing is MS fatigue is different from general fatigue in many people.

The second thing is I keep on saying don't think about fatigue as a simple thing but ask the questions as a clinician -- or as a patient about where the fatigue comes from. So, in addition to MS fatigue, we might say, there are things that people experience and maybe even more so people with MS that add to fatigue that are treatable.

So, if people are having bladder issues that don't allow them to sleep a full night and they're up at all hours, not sleeping, that's going to increase fatigue, a reason to pay attention to bladder - a urologist.

Some people fatigued because of the medicines they're taking, including the benzodiazepines for muscle spasm, including some of the other agents that we're using may increase fatigue, the medications used for pain may increase fatigue. It's worthwhile to look at the medications and see whether they could be playing a role.

Number three, if there is depression going on and depression goes on common in MS, if they are saying, yes, anxiety going on, and anxiety is common in MS, that can increase fatigue, all the more reason again to start to pay attention to mental health. And if there is significant anxiety or depression, to go for -- that's a treatable disorder. Both are treatable and a reason to treat.

As I go through these things and say, pain is fatiguing. Insomnia is fatiguing. Bladder dysfunction, therefore, can be fatiguing. Medications can be fatiguing. Depression can be fatiguing. Anxiety can be fatiguing. It is important not just to say I got MS, I'm fatigued, but to try to look for other things which may be adding to it that are treatable.

Number two, MS fatigue is treatable and will -- we use a lot of agents with some partial success, the Provigil, the Nuvigil, et cetera, et cetera. But what -- the question was predicated on exercise. And so, I would say, it's part of the wellness routine we believe that exercise is actually important. We believe the diet is important for fatigue. Obesity adds to fatigue. Healthy diet reduces fatigue.

We think that that exercise reduces fatigue if it is approached properly. What I wind up saying to people in my practice, if I told you go out to run or walk half an hour or an hour, you, A, might refuse to do it; and B, if you were willing to do it, you might be in bed for the next three days. And so, it's important to begin with a very, very modest exercise program that you're willing to do. If your person is willing to swim but not run, then swim. If your person is willing to do a treadmill at home but not go outside, that's what you should do. If it's upper body exercise that's more appropriate, that's what to do.

So, find the form of exercise that works for you. Do start out with modest increments and then build over time. If you try to start out full force, you will create fatigue. If you begin with slow increments, something you are willing to do and keep it that you like doing, it should reduce fatigue in many people. But there is no magic bullet or one one-size-fits-all. And even when we treat the fatigue of MS, it's not that we make it go away. It's that we mitigate it. But there are a lot of strategies, don't be superficial and don't be pessimistic.

Gina Murdoch: Thank you. Another question we've had a couple of times is, how do you know that the medication is really working?

Barry Hendin: So, you -- so, it's hard -- so it's a question that I think is actually hard to answer. People who are doing well will say to me, I'm doing well, but might be doing well even if I weren't taking the medication. Yes, it's true, we don't know in individuals.

So, in population, we know the medications work. The disease-modifying therapies wouldn't be available if they hadn't passed scrutiny, scientific scrutiny and been approved by the FDA. In the individual, it's a little harder, but I would say my gauge, my litmus test, for is it working is the following. If you're not -- if it's a medication that's anti-inflammatory and you're not having the signs of MS inflammation apparent and that means you're not having relapses and you're not having new MRI lesions, then we presume that the agent is working.

And the data tells us that people are doing better now that we started agents, the disease-modifying therapy than they did 20 years ago or 30 years ago or 40 years ago, certainly better than they did before we had these agents, also better than they were doing before we had more effective agents.

And so, we know in populations they work. In the individual, my question is, are you having attacks? If you're having attacks, it's not working, at least not optimally. If you're not, it's doing what I want. Are you having rapid progression? If you are, it's not doing what I want. Are you having new MRI events? If so, it's not doing what I want.

We have lots of choices if they're failing. But if you are stable and your MRI is stable, then the assumption has to be it's probably working. And I don't want to find out the opposite by getting at least during your early years with MS. When a person is very -

- I am sufficiently senior neurologist to say, there's an agent which I think we can ask the question that is, is still working at my age and do I still need it? That was an earlier question that I try to address.

Gina Murdoch: Thank you. There was one question and the person said, they've been told to take vitamin D by their neurologist and they have been taking D3 for a while. And what would be the difference between D and D3?

Barry Hendin: So, I was actually -- I became interested in vitamin D in the 1970s and remained interested in vitamin D ever since that time. I think we got good evidence that people who have higher levels of vitamin D in their blood do better than people who have lower levels of vitamin D. We mostly believe that giving vitamin D is appropriate, although some of us note that we don't -- we never subjected this same kind of scientific rigor that we -- that we devoted to the disease modifying therapies.

So, most of us who treat, treat with vitamin D and the way we determine whether it's the right vitamin D is blood level. Normal blood levels in most labs are 30 to 100 units. I tend not to care what formulation of vitamin D you get -- you need -- you use to get there. I tend to like people in the higher range between 50 and 100. A lot of my patients are on 5,000 units a day, but not all. And I take a blood test at least periodically to see whether I kept them in that range. And with the sense that vitamin D is probably helpful in MS and certainly is a good thing for people and their bones additionally. But again, I don't care the formulation. I care more about the blood level.

Gina Murdoch: Wonderful. There's one more -- and I think we have time for one more question. Is there anything other than Botox or Ditropan to stop incontinence? This person has tried both and have had not had great success.

Barry Hendin: So, I think there are a wide variety of things that can be used for mild or moderate or severe bladder dysfunction. For mild dysfunction, they can be the medications, the Ditropan, the Myrbetriq, et cetera, et cetera. My sense first is that when a person is having incontinence that the neurologist should be sending them to urology so that they can have a proper evaluation of bladder, cystometrogram, so that we know why the bladder is problematic.

And how we address the bladder depends on what was really causing the incontinence. Sometimes it's a very large bladder with overflow incontinence or a very small overactive bladder that's causing incontinence.

So, number one, if there's incontinence, we need a urologist and we need to understand the physiology of the bladder dysfunction. Once we understand that and there are a wide variety of things that can be done addressed to the specificity.

In more severe cases, Botox can be used. Simulators can be used. But the urologist really do have variety -- and I -- and clearly some people are using intermittent catheterization, et cetera. If I summarized, I would say again there's no simple answer to incontinence, depending upon why the incontinence. The neurologist will not be able to answer that as well as the urologist without a bladder test, cystometrogram. Once that's done, then the options become clear.

But for some people, it really is that -- it's Botox. For others, it's stimulator. For others, it's intermittent catheterization. That's a discussion with your urologist.

Gina Murdoch: Wonderful. Well, we are at the top of the hour. So, that will conclude tonight's webinar. I would like to once again thank Dr. Barry Hendin for his insights in the MS landscape. I would also like to thank our funding partner, Novartis, for providing support for this program.

As mentioned, tonight's webinar will be archived to our website and we ask you to take a very brief survey that is coming up next. Our funding is really dependent on our evaluations. So, please take just a couple of minutes to answer a few questions for us.

On behalf of MSAA and Dr. Hendin, we thank you so much for joining us this evening.

Dr. Barry Hendin: And thank you.

END