



“What’s New in MS Research: A Look Into the Future of MS Treatment”

Presented by Barry Singer, MD

Kyle Pinion:

Hi everyone. Good evening, good afternoon, or whatever equivalent you might have from where you're watching right now. Welcome to the Multiple Sclerosis Association of America's live webinar "What's New in MS Research: A Look Into the Future of MS Treatment." I'm Kyle Pinion, Senior Director of Education, Healthcare Relations, and Advocacy for the Multiple Sclerosis Association of America and your host for tonight's program. Hooray! On behalf of MSAA, and our presenter, we greatly appreciate the opportunity to keep you updated on this very important topic and please know that we hope you and your family are staying safe and healthy in these uncertain times.

MSAA is extremely honored to host this educational program with Dr. Barry Singer, Director and Founder of the MS Center for Innovations and Care at Missouri Baptist Medical Center. As I'm sure you know, MSAA is a national nonprofit organization dedicated to improving lives today for the MS community, now in over a half century of service to this incredible population. 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. It's free – you can't beat that.

Also, please know MSAA has expanded our helpline hours to 8:00 PM Eastern between Mondays and Thursdays. To learn more about these, and all the ways MSAA improves lives today, please visit mysaa.org or call 1 (800) 532-7667.

And one quick plug – we have a brand new publication called "It's a Generational Thing." A toolkit designed to aid communication between parents and children, be it a parent living with MS, or a child living with MS. We think it's something you'll find very valuable, and a perfect compliment to our already wonderful Mommy and Daddy's Stories booklets. Please check it out on our website when you get a chance. I think it is fabulous and I think you will, too.

Additionally, I wanted to draw attention to our brand new Virtual Display Hall, which you probably heard us discuss a little earlier before the program started. This has been made available thanks to the generosity of our selection of sponsors. If you haven't already, please take a minute to click on the link in the chat box to visit this new and exciting information portal, which showcases the products and services offered by our sponsors and we want to thank our friends at Biogen, Genentech, and Sanofi Genzyme for their incredible support.

Lastly, please know that tonight's program will be archived to our website very soon. For our Q&A session, please type your questions into the Q&A box and we'll address them at the end of the presentation, time pending. I will tell you we received so many wonderful questions at the registration process time, that we may not get a chance to get to all your questions. But, we're going to do our best and certainly hope to be able to address them in a timely fashion. Also, if you have any technical issues at all please type those concerns into the Q&A box, as well.

Lastly, when the program is over, please make sure to fill out our survey, which may already be populated on your screen, but we'll also link it in the chat box so we can get all of your opinions and thoughts and making sure that we develop programs that are relevant and interesting to you as someone living with MS, or a loved one supporting a member of this community.

Now we are so pleased to have you join us for this timely conversation and I am honored to introduce Dr. Barry Singer. Dr. Singer earned his undergraduate degree from Duke University and his medical degree from Columbia University College of Physicians and Surgeons. He completed his residency training in neurology at New York Hospital Cornell University and the Neuroimmunology Fellowship at the National Institutes of Health. Dr. Singer is the Director and Founder of the MS Center for Innovations in Care at Missouri Baptist Medical Center in St. Louis. He is an Associate Professor of Clinical Neurology at Washington University School of Medicine, he has been an investigator in greater than 35 multiple sclerosis trials focused on new therapeutic options, including remyelination. So I got to tell you, we got the right guy for this talk.

He serves on the Board of Directors of the Multiple Sclerosis Association of America since February 2016, and has a position on its Executive Committee. Dr. Singer has received a Congressional Proclamation for MS research in 2008, and his award-winning MS patient education website www.msivingwell.org I'm going to say that again, www.msivingwell.org started in 2007, has been a valuable resource in 200 countries. Dr. Singer is also the host of the MS Living Well Podcast, which you can find on iTunes, and I even found on Spotify. So if you're a subscriber on Spotify, check that out. I'm so happy to introduce my good friend - and one of the greatest advocates for MS care in the world - Dr. Barry Singer.

Dr. Barry Singer:

Hey thanks Kyle! Hey thanks so much for inviting me, it's great to be with everybody this evening.

Kyle Pinion:

Yeah, no it's fabulous to have you and thank you so much. I hope you had a great Fourth of July holiday.

Dr. Barry Singer:

Yeah, I was on call actually I was covering the hospital but that comes with the territory, so that's part of being a doc.

Kyle Pinion:

I get it, I get it. Thank you for all your service for the MS community and beyond. Now before we get started, I just want to explain how this program is going to work. This is going to be a bit of a conversation between Dr. Singer and myself, which would make this I think pretty fun. Consider me like your Conan O'Brien to Barry Singer as a celebrity guest, if you will. Before we get

started, we do have a polling question that I want to get us all sort of excited and revved up for first.

So the very first question I want to ask is, which superpower, if you could have any superpower, would you like to have? I'm going to launch that now. I'd love to see what y'all's feedback is on this. This is just a fun warm-up question. I already know what I would pick, Barry. I got to be honest with you, it would definitely be super speed for me. It would have to be. Mostly because I can get...

Dr. Barry Singer:

I think I'd take flight.

Kyle Pinion:

I gotta tell you, based on the results I'm seeing that it seems like most people would pick that, too. You know, with super speed you can go into the past, and you can like, go and mess around and time travel. I've watched enough Flash on the TV to know what all the fun stuff he gets up to.

Dr. Barry Singer:

If you're living with disability, I could see flying would kind of solve a lot of problems there. A physical disability, at least.

Kyle Pinion:

Sure, super strength would be fun, too, actually.

Dr. Barry Singer:

I think we should have a write-in here.

Kyle Pinion:

I know! Well, with a minute to go here, I think we've gotten quite a few votes, so I'm gonna end the poll here. Here are the results, let's take a look at them. Look at that, "flight" and "super strength" tied! Some real diverse perspectives on the superpowers people should have. Thanks for humoring me folks. So let's get started and let's actually like get to the fun parts of the conversation, and let's talk a little bit about the most recent FDA-approved treatments for MS. Dr. Singer what are they, and what can you tell us about them?

Dr. Barry Singer:

So, for the past three years we've seen like incredible progress, in terms of the amount of options. In fact, it's almost dizzying amount of options when you have a newly diagnosed patient sitting in your office and we're talking about where do we go. It's great to have all these new options. You know, when you think about it, there was no treatment before 1993, and the first oral didn't even get approved until 2010 – FDA approved. So now we have an array of options. So let's kind of dive in.

Most of these are for relapsing forms of MS, so this would include people that had their very first attack given let's say optic neuritis – visual loss in one eye – with lesions on the brain, consistent with MS. Relapsing-remitting people having attacks and getting better, and then those that are slowly getting worse: secondary-progressive. Most of the drugs are approved for secondary-progressive that still has relapses, or still has MRI activity. So you're more in the

progressive phase, but there's still relapses or new MRI activity and we call that active secondary-progressive MS.

What are the new options? One class of drugs that we have are called fumarates. Many of you are familiar with Tecfidera® and the generic version dimethyl fumarate that got approved. We have actually two new compounds in the same class, one is Vumerity™. Vumerity tends to have, it's a diroximel fumarate and it's converted into dimethyl fumarate, which is the active ingredient of Tecfidera. The advantage of it is less gastrointestinal side effects. In fact, I was involved in the clinical trials and we found that less than one percent of patients discontinue the gastrointestinal problems on Vumerity, compared to about 4 percent, 4.8 percent of patients on Tecfidera. So, a little bit better tolerated fumarate. Then there's a monomethyl fumarate, which is Bafiertam™. It also just got approved, as well. So we got diroximel fumarate, dimethyl fumarate, and monomethyl fumarate.

Another big class of MS medications that's kind of exploded are called the S1P medications, and these are oral medications that can be taken once a day. Many of you are familiar with Gilenya®, that's been around since 2010. One downside with Gilenya is you had to monitor people for six hours doing blood pressure and pulse check when you first start, because of rare heart rate issues, so we had to monitor patients. We don't have to do that with these new options. They all start with a titration up. One of those compounds, the first one that got approved is Mayzent®. Mayzent was studied in progressive patients. These were patients, and generally a little bit older than a relapsing-remitting clinical trials. 56 percent of people needed assistance; the age went up to 60 – so we looked at an older population that was more progressive. Actually very few patients, a very small percentage of patients were having new active lesions or new relapses, and it slowed down the progression in that group of patients. So positive in the secondary-progressive category, approved for active secondary-progressive MS, relapsing-remitting MS, and clinically isolated syndrome.

There's two other S1Ps. One is called Zeposia®, and Zeposia, not only is approved for MS, it just got approved for ulcerative colitis. I got a few patients that got both, so now they got one option that killed two birds with one stone. This clinical trial was compared against Avonex®. There was a couple trials. In the two-year trial, it reduced new relapses by 38 percent compared to Avonex. Then the most recent S1P approved is Ponvory™, and Ponvory is a once-a-day pill, as well. It was compared against Aubagio® and cut relapses by 31 percent. It's great to have three new options in the S1P class. Now I'm going to transition...

Kyle Pinion:

I was just going to ask, I mean there's so many therapeutic options and I feel like with 19, I think it's 19 not counting generics, how does a physician choose the right one for the right patient at that time?

Dr. Barry Singer:

So, a lot of it, you have to kind of look at the disease, you know. Does someone have very active disease, you know, are they having a lots of relapses? Is someone with more relapses early on the disease course, we may get a more aggressive treatment. If you've got a lot of lesions on your brain, we may want to take something that may be more highly effective than someone that has two or three lesions in the brain and maybe nothing in the spinal cord. So we look at the disease, how active is the disease?

We also have to look at the individual. Where are you? Are you someone that's ready to have a baby and may be coming off treatment, or do we need to find something that you can

take actually during pregnancy? Is this someone that's 60 years old, and you have to worry about the immune system not being quite as robust and there's an increased risk of infections, or maybe even cancer, we have to kind of look at the individual. Some patients, unfortunately, we know that African-American patients are at increased risk for disability, so we may want to be more aggressive with treatment. And men tend to do worse. We try to look at who the individual is. All those factors come into play. We also look at other medical conditions, so sometimes if you have GI problems, one class may not be good. If you've got diabetes or maybe a risk with another class, so we really look at the medical issues, as well.

Then the final couple I want to mention, two other new medications that are out there. One is Mavenclad®, and that's a oral medication, you take it for four or five days. A month goes by, you do it again and then you're good for a year. You do it again year two, and then no treatment in years three and four. That reduces relapses by about 58 percent, kind of resetting the immune system. Then, finally we have Kesimpta®, which is very similar in terms of how it works as Ocrevus™, some of you are familiar with that. Instead of an antibody in the IV twice a year, you do an injection once a month under the skin at home. This was very positive, it reduced relapses by 51 to 59 percent versus Aubagio.

So a lot of different options out there and it's really important that you know about your options, but sit down and your neurologist may kind of shrink those options down to two or three and talk about pros and cons that might fit for you.

Kyle Pinion:

Sounds great, but I guess in the look of the future, looking into your crystal ball, I'm curious about what treatments are in development for – I guess we'll break them down into the two blocks of MS, I mean even though there's four – but we'll just say relapsing and progressive. Let's talk about relapsing first. What treatments are in development for folks who have relapsing-remitting MS right now?

Dr. Barry Singer:

Sounds good, why don't you hit the next slide for me? Relapsing disease – so are there new therapies for relapsing disease? So, there are a lot of things in clinical trial and development. The one that's probably that the data's already been out there, presented is another B-cell depleting medication, so it's an antibody infusion twice a year. It's got a big name called, ublituximab. So ublituximab was also compared against Aubagio. It's easy to go against an oral once-a-day, you know, in terms of an oral once-a-day that's well tolerated, so it's easy to set up those clinical trials. If you look at the patients on ublituximab, it dramatically reduced active contrast lesions of the brain by 96 to 97 percent compared to Aubagio. It's important to keep in mind, Aubagio already prevents 80 percent of lesions, so this is 96 to 97 percent better. One-hour infusion, which will be very convenient for patients. They come to the infusion center and, after the first one which is more prolonged, after that it's a one-hour infusion every six months. It's very convenient.

Then, we have another class of MS medications. It's being studied across a spectrum of disease, from relapsing, to primary-progressive, to secondary-progressive. These are called BTK inhibitors or Bruton's kinase inhibitors and, so these BTK inhibitors affect two cells. One is the B-cell, but instead of knocking out B-cells for six months it's a more shorter acting, so potentially, if you discontinue the drugs, the B-cell function can improve. But, these BTK inhibitors also target a cell called microglia, and microglia seems to play a role in progressive disease. We see in people with MS, inside the brain and spinal cord there's some lesions or MS plaques are still smoldering information around the rim, so around the rim there's this group of

microglia cells that are causing inflammation. These drugs really, not only target the B-cells, but also target the microglia, so there's some hope that these drugs may help slow down progressive disease.

The ones that are looking at relapsing MS right now, are evobrutinib, which was studying a Phase II clinical trial. The 75 milligrams twice-a-day dose seemed very effective on reducing new active lesions and a trend of reducing relapses, so that's headed into a Phase III clinical trial program. Then tolebrutinib was also studying Phase II trial, and it prevented about 85 percent of the active lesions on the brain and 89 percent reduction of T2 lesions. So, very robust results, and that is now being studied in relapsing MS, secondary-progressive MS, and primary-progressive MS. Some of these agents are out, a lot of different options. One last relapsing trial that's out there is a medicine called a neuropeptide – a combination of two compounds it's called Enkorten® and that's in Phase III clinical trials. There's a lot of, some new options for relapsing MS, we've got a lot of options for relapsing MS as it is, but there's some new options for relapsing MS.

Kyle Pinion:

On follow-up to that, earlier on you mentioned one particular therapy which had benefits beyond delaying progression. I know Zeposia is one of these therapies that has kind of multi-factor benefits. I'm curious are any of the therapies that are in development have that same sort of benefit for patients?

Dr. Barry Singer:

We're definitely looking at across the spectrum not only, so the original outcomes that we looked at the clinical trials so many of you that are familiar with the traditional drugs for MS, you know the interferons and what we always looked at was the reduction in new relapses. Does it slow down the progression of disability? Does it prevent new MRI lesions? Some of these new agents, what we're really looking are we're going beyond that.

You know, one of the things we're concerned about in MS is the brain tissue can shrink over time and we know this happens at a faster rate. Typically with MS, this happens somewhere between 0.5 and 1.35 percent per year, so there's definitely some brain shrinkage. In many of our new medications we're looking at preserving that and preventing brain shrinkage, which can affect you cognitively and physically. So really, the goal in some of these medications we're looking at brain volume.

We're also looking at something called NEDA, which means No Evidence of Disease Activity. We're trying to stop relapses and new MRI activity and disability. In my office, I like to call it "boring." I want boring visits! I want nothing going on, MRIs unchanged, they're not getting worse, everything's good. NEDA, No Evidence of Disease Activity, is another thing that we're looking at. Even in clinical trials, we're also looking at clinical disability improvement. We're seeing in some of our highly effective medications that things are actually improving over time. That's definitely some of the outcomes that we're looking at. It's not just the traditional ones that we originally were looking at so now the bar is being set higher, can we get better outcomes?

I think the other big area that, one of the other things we're looking at is how can you intervene earlier? There's some new concepts looking at this. One, it was interesting, in the University of Calgary, one of the insurance companies was not covering after your first attack with lesions in the brain, they were not covering treatment at that point. So they came up with a trial, they're looking at minocycline, which is an old antibiotic that not only has some anti-inflammatory benefits, and has been around for a long time – it's actually used for acne – minocycline is now,

there's some preliminary trial data that shows some positivity and so now it's being studied in a larger trial at the University of Calgary to see does it work to prevent conversion into definite MS? It would be great to have an inexpensive, easily accessible medication globally to prevent conversion into MS.

Kyle Pinion:

No kidding! Wow, that's incredible. Let me ask you though, on the progressive side, I'm sorry I don't mean to interrupt, you know, I'm curious about on the progressive side. I know we have Ocrevus for primary-progressive patients, but is there anything new that's being developed for that particular population?

Dr. Barry Singer:

Particularly for the primary-progressive patients, there are some clinical trials. It's actually, before I prepared for this, I went and looked at clinicaltrials.gov – great website – and you can see, actually any clinical trial, you can find out what sites are recruiting for the clinical trials, but over 400 clinical trials globally are now actively recruiting for people with MS to participate. An array of, not all of them are you know, like interventions or medications, some of them are monitoring disease and looking at disease. For the primary-progressive MS, there's a few trials specifically for the PPMS. One is, two of them are in that BTK inhibitor, so one is tolebrutinib and there's another one fenebrutinib, and so these are, because they affect that cell, that microglia that causes that smoldering inflammation, there's some hope that these drugs will help slow down primary-progressive MS. As you mentioned Kyle, only Ocrevus is now you know FDA-approved for primary-progressive MS and that was based on the ORATORIO trial.

There is glatiramer acetate, which is Copaxone®. There's a form of GA that's being injected monthly and that seemed to have some promise. Then we have a group of drugs that are looking at, they're being studied in both secondary-progressive and primary-progressive MS patients. There's a lot of overlap in these secondary-progressive people without relapses to primary-progressive, things are slowly getting worse. There's some options there. One of them is being studied in both populations is lipoic acid, and lipoic acid has anti-inflammatory and antioxidant properties, so there's a study going on right now in about 119 patients looking at lipoic acid which would be inexpensive, easy, hopefully trying to slow down the progression. There was also data in a pretty large trial of an oral medication called masitinib. Masitinib was studied in 301 patients and it really reduced the likelihood of disability progression. That's an exciting compound that's now going into a larger clinical trial, so another exciting advancement.

Kyle Pinion:

Outstanding! I know you answered this a little earlier, so forgive me. I want you to reiterate it though because a few people have asked this question in the Q&A, and I think it's important. The FDA has approved certain therapies for secondary-progressive MS, and others for what's termed as active secondary-progressive MS. How do we define the latter, and can either therapeutic option be a benefit to patients with primary-progressive MS, by chance?

Dr. Barry Singer:

So really, everything that's approved right now is for active secondary-progressive MS. None of them just say pure secondary you know, the drugs that we have available are not pure secondary-progressive MS. I think the closest one you know if you look at the data from Mayzent, from the EXPAND clinical trial, most of the patients were not active secondary-progressive MS.

So what's active secondary-progressive MS? Let's say your leg is slowly getting weaker, your balance is a little worse, you're slowly getting worse over time. Where you were six months ago, a year ago, you could see slow progression but you still have a relapse from time to time. You still may or may not have new MRI activity. It's active SPMS, as if you're still having new MRI activity or still having relapses superimposed. The hard thing is if you're on treatment, so you're started on an MS medication you may be suppressing some of that activity. Until you stop it you don't know if you're really active SPMS or not. That's a challenge, in some countries you know, trying to make a decision with an individual patient. Those are the drugs that have been approved, really for say active SPMS to shut down that information. You know, there are some other very exciting fronts on for secondary-progressive MS.

One of them is simvastatin. Cholesterol drugs have been studied in MS for, actually, a lot of years and there was a trial adding it on to Rebif® and Avonex back in the day, but there's a very large trial going on right now with over 1,100 patients in the UK looking at simvastatin, a cholesterol statin medication that has anti-inflammatory properties. Hopefully, that may show positivity and that would be an inexpensive trial. There's even like a cool clinical trial looking at, it's called T-cells, which are one of the immune cells – T-cell receptor vaccination. So, there's a trial with that and the idea with the vaccination, is you're trying to create cells that suppress autoimmune disease. There's cells called regulatory T-cells and they keep autoimmune disease in check, so this is a vaccine to pump up these regulatory cells to keep autoimmune disease. This is being looked in secondary-progressive MS, so there's definitely quite a few things that are going on, some interesting approaches to trying to control SPMS.

Kyle Pinion:

Wonderful. Well, let's talk about the hottest ticket in town. I feel like every time we have a talk like this, everyone wants to talk about remyelination. I think that really does hold a lot of promise for patients, but how is that research going, currently?

Dr. Barry Singer:

There's pros and cons. I kind of look at it there's battles and then there's a war. I think this is doable, I think we can definitely stimulate myelin. There's cells in the brain called the oligos, and those are the mature cells that make myelin. We know in the brain and spinal cord 5 to 8 percent of the cells are these immature myelin-making cells called OPCs. These immature cells, the idea is to turn them on, recruit them into the plaques, create new myelin. There's been approaches with that – in fact, I've been involved in four or five, actually five clinical trials where we've tried antibody therapies to try to stimulate remyelination. One of them was opicinumab, which was studied in a number of clinical trials, with some early evidence that it might work including in optic neuritis. But another clinical trial failed so, that's not going forward.

Then I was also involved in some Phase I clinical trials, early stage, with a compound that was developed at the Mayo Clinic with Moses Rodriguez called rHlgM22. We've been trying some things early on, but the antibody therapy so far, nothing's hit. There are a number of exciting advances, though, going on in clinical trial. One of them is a clinical trial looking at 150 people that have optic nerve damage, and they're giving them nanocrystals of gold. So, the idea is gold therapy. It's oral, and actually there's animal models that it can get in and stimulate, turn on the metabolism of oligodendrocytes – these myelin-making cells in the brain – and make myelin. So, pretty cool. There's a trial going on with 150 people with crystalline gold.

Then there's the trial on remyelination out in Portland, at the Oregon Health and Science. They're looking at stationary exercise bikes and seeing if aerobic exercise actually stimulates myelin production, and they're doing some electrical tests to show that. Speaking of

electricity, in Paris, which is, France is a big area of remyelination research, they're actually giving electrical stimulation right to the eye, outside the eye, to people that have optic neuritis, to see if that can stimulate remyelination. Then we have compounds they're looking at. Actually, there's some evidence that testosterone increases remyelination, so there's a study in France of injecting testosterone. I assume, this isn't guys, it doesn't say on the clinicaltrials.gov website but they're injecting testosterone to see if that increases remyelination.

Then finally, a center that's done tremendous amount in the field is at University of California San Francisco. Jonah Chan has done these cool little, he's created these micro pillars, which are like cones, and you stick one immature myelin-making cell on top of it. Then these cones, they're called micro pillars, there's a whole tray of these with all these little cones that you can add all these old compounds on – approved medicines on top of that – and see what grows, what stimulates myelin production. A couple compounds have come out of this. One is clemastine, which is a clemastine is a anti-histamine medication. That was studied in optic neuritis, seemed to have some benefits, so that's being looked at. Then bazedoxifene is looking at 50 patients and this is an estrogen modulator. It's interesting, so now you can find compounds that are out there – you don't have to reinvent or create a new drug – and see if they work in a myelin-making trial.

Kyle Pinion:

That's super interesting, especially about the testosterone trial. It sounds like sort of the opposite of the estriol trials from many years ago. That had always sort of stuck with me, and people are always asking about testosterone trials, so I'm fascinated by researchers kind of diving into that area.

Dr. Barry Singer:

Actually, estriol trial is still around. So estriol trial looked at added to glatiramer acetate, Copaxone back in the day, and it didn't seem to add much benefit. It actually is being looked at cognition. So, this is a hormone that's actually produced in the last trimester of pregnancy at high levels, and it's interesting – so women with MS do really well in terms of the MS disease in the last trimester. The disease tends to be quieter, so the idea is to give estriol trial to see if it helps with cognition and MS.

Kyle Pinion:

Very good. Well wonderful! So, in terms of when we might actually see remyelination produce a type of treatment, or even a more loaded question, what can we actually expect that it might restore for a patient, vis-a-vis mobility or quality of life, is there any sort of long-shot answer for that?

Dr. Barry Singer:

I think there's two components to it. One, obviously, the ultimate goal if it works robustly, is you could restore a function, so improving function. That's the great hope. That if you can robustly turn on remyelination, you can remyelinate some of these plaques. Many of the axons and nerve processes are just not covered in myelin, so if you could stimulate that and recoat the nerves, you could theoretically improve function. Another aspect of it is, when these long nerves like some of your nerves go from, your neuron goes from your brain your cortex all the way down your spinal cord, some of them are very long and they're covered in myelin.

Myelin not only helps electrical conduction down the nerve, but also supports that axon and protects it, and nourishes it. So if you lose the myelin, then that nerve over time is at risk for

dying or getting injured, and that may lead to progressive MS. The idea is if you could recoat, maybe you would protect those axons long-term so that when people get in their 50s and their 60s, they're able to maintain their function and not develop progressive disease. It would also be kind of stabilizing the disease and preventing what we call neurodegeneration, or the loss of the axon over time. So, kind of a protector. Both of those are reasonable goals, but you know, you just got to keep slugging away. We need, for those pharma partners that are tuning in tonight, we need you to invest in remyelination. I got the patients, and I'm sure plenty of you out there are eager to sign up for remyelination trials. We all have to partner together to try to advance the ball. I think this is doable and I think eventually we're going to find something that that's going to help remyelinate.

Kyle Pinion:

Well, to pivot to symptoms – you know talking about MS symptoms is its own presentation in and of itself – but in terms of recent advancement in managing MS symptoms, are there any particular highlights you'd love to discuss?

Dr. Barry Singer:

I can talk about some of those trials, if you want to flip the next slide. There's tremendous amount of symptoms. I think one of the best things I do, particularly patients with more progressive MS, I think one of the greatest things that I do in the in the exam room, is work on trying to improve quality of life. There are many symptoms of MS that we can do things about – spasticity, nerve pain, fatigue – so there's a lot of things we can treat. There are some, a lot of research going down, on looking at different options.

One of the cool trials that's going on – fatigue is like number one, 90 percent of people with MS have fatigue. So there's a trial going on called COMBO-MS and there's growing data that people that get cognitive behavioral therapy can actually reduce their fatigue level. There's a lot of clinical trial data that shows that cognitive behavioral therapy really helps. Unfortunately, there's not a lot of CBT going on right now for people for fatigue. Tends to be energy conservation, managing it, working on sleep, and then drugs. So this trial, the COMBO-MS, looks at cognitive behavioral therapy, they look at modafinil, also known as Provigil®, and then the combination to see what works the best for people with MS in terms of reducing fatigue.

There was an interesting study of looking at fatigue, where patients were randomized to, they started on either amphetamine, amantidine, Provigil or then they went on to placebo, and everybody, all patients, took all four different options and they didn't see a significant difference between all four. Which is kind of surprising, because many of my patients, and many other clinicians I know see significant benefits from some of these medications.

A few other things that are being looked at, bladder is a big issue for a lot of patients. There's tibial nerve stimulators, where you stimulate a nerve in the leg to try to improve the bladder function. This is being actually studied directly in MS patients.

For spasticity, in Europe there's a compound nabiximols, which is a cannabinoid product, is being studied and that's now going into clinical trial in the United States to look at it for spasticity in people with MS. There are a lot of different symptomatic treatments out there, medications out there. Unfortunately, we need more, probably more clinical trials looking at interventions that could work to improve some of these aspects of people's quality of life.

Kyle Pinion:

It always surprises me, too, to learn about, spasticity especially, because you know, about 10 years ago I learned for the first time that Botox® was a treatment for spasticity. That just absolutely blew my mind, you know, considering what Botox is typically used for, as anti-aging remedies. It's interesting that it's used for something that's so life-changing, as well.

Dr. Barry Singer:

Yeah, I mean we, actually, we use Botox. A lot of patients get it for migraines so, you know, MS – the average age is 20 to 40 and newly diagnosed. So migraines are common in the population, we use it for that. We use it for something called a hemifacial spasm, which could happen in MS. We use it for bladder urgency, so bladder can be a lifesaver for people with Botox. I saw people today that it was just life changing, they went from being – we have to wear undergarments to completely dry, so we use it for that. And we also use it for spasticity, and so yeah, it's used quite frequently. It's one of our options.

Kyle Pinion:

Well to get away from symptoms and to sort of move into the wellness space, what can you tell us that research sort of informs us, regarding exercise and diet in MS, currently?

Dr. Barry Singer:

This is a huge area that we really need to focus on, together. I think it's very important if you're living out there with MS that you really sit down and talk to your providers and come up with a game plan here. I did that a lot today with my patients. So diet, so what's the right diet for MS? I think this is a million-dollar question. There was an interesting, just a recent trial, it was a small trial, sponsored, Terry Wahls was the lead on that. It was looking at the Wahls Protocol, which is like a modified paleo diet, versus the Swank diet, which is a low saturated fat diet that's been around for a long time. They looked at, what started out at about 100 patients, but ended up with about 85. They kind of looked at people on a regular diet, switched on to these diets. Of course people knew they were switching, but they seemed to have some improvement in fatigue and quality of life. Then, if you follow between the two groups there was some benefits for Wahls over the Swank diet at some endpoints, but it was small, unfortunately, a small study to really prove things.

Generally, when I talk to my patients, I talk about the perimeter, which means you go in the grocery store, you skip the aisles, and hit the perimeter. I like fresh fruits and vegetables, dairy's okay, it's got some Vitamin D, lean protein, and then skip all the unnecessary carbs and packaged foods. Kyle's getting sad. I don't know what's on aisle five for you, but there's something in there. So, diet's important. There's also some really cool stuff on nutrition being looked at. Intermittent fasting has been shown to have some benefits in autoimmune disease. Here in St. Louis at Washington University, there's a trial looking at intermittent fasting to see if there's some benefit from that.

There's also this cool idea that your microbiome – your gut, the bugs in your gut, basically – affect your immune system so tremendously. There's a lot of research going on looking at your microbiome. Even, I don't know about you on the West Coast, you're still having dinner, but there's even a study going on in fecal transplant multiple sclerosis. This has been used in people with C. Diff. Colitis, which is pretty nasty inflammation in the colon that you could get after being on antibiotics. So, it's a treatment for that. They're actually looking at it see if it proves things in MS. A lot of interesting things going on that front.

Kyle Pinion:

I've even seen studies about the Mediterranean diet for MS patients in Italy, and the benefits that may or may not have for an MS perspective.

Dr. Barry Singer:

I think there's a lot of interesting things, and we need more funding for it. Because, unfortunately, it's hard. Sometimes this gets not funded as well and really to prove things in MS is very hard because you need hundreds of people, if not thousands of people, in clinical trials to prove things. It gets a little hard to know. I have many patients that take supplements. I mean, the one we know definitely makes a difference is Vitamin D, and there was a nice trial with Betaseron® that was looking over five years, and people with higher levels of Vitamin D had less MRI activity, less relapses, less disability, and you could kind of group them out. It was five different groups and so the people that had the highest amount of Vitamin D had the least amount of activity. Having good Vitamin D levels is really important.

Kyle Pinion:

Well folks, you heard it here: lean meats, vegetables, produce aisle, milk. When you're doing your Sunday grocery shopping trip.

Dr. Barry Singer:

Healthy living and then exercise. So exercise is really important. Use it or lose it. It's been a little crazy with the pandemic. I have to say, I haven't been in the gym since March last year. For many of my patients it's been a huge issue because can't go to the pool you know some of people with a more advanced disability like water aerobics and group exercises. A lot that's been on hold because of the pandemic, so really got to figure out where you're going to go with the game plan. Actually, my one of my last patients has been going to the gym after they've gotten vaccinated, so you kind of have to figure out a game plan in terms of what works for you.

The most important thing is consistency. Show up every day, or if you're doing three days a week, just keep doing it. Even if you have a bad day, and you can only do the bike for 5 minutes instead of 25 minutes that day. Just get out there, kind of keep doing it. Find what you love, find what you're passionate about. Talk to your doctor, what's a good option? Obviously, we don't want doing things unsafe. So, if your balance is bad, don't use a treadmill, use a recumbent bike. Try to figure out what's going to work well for you.

The other important thing is brain health. This is a huge, important area. What helps your brain? Brain is helped by good sleep. If you're not getting good sleep, we need to work on it. Your concentration, your focus, is not going to be good. Smoking is a horrible thing with MS. Smokers end up with more disability both, not only physically, but cognitively, so memory, multitasking problems, word finding difficulties. It's slowly progressive disease. I saw patients today, they really struggle with that. So, you got to work on ways to stop the smoking, because smokers end up with much more disability. You can be on a highly effective MS drug, but then you're hurting yourself with smoking, so really work on that. Then other diseases that can affect the brain include hypertension and diabetes, so we really want to get those conditions under control and really manage those so that way you can have as much brain health. Clearly we don't want new lesions on your brain. So the more we can control the disease, the better off you're going to do. Exercise is important, as we mentioned. Diet's important. So we really want to keep your brain healthy so that you can age well. You want to be involved socially with other people, you want to connect, you know, so I think this is all important for positive brain health.

Kyle Pinion:

Agreed and you know, that leads us very wonderfully into our second and last polling question, which I am going to launch now I believe. Yes there we go! What type of health and wellness topics are you interested in learning more about? I can't wait to see what people have to say, because this might actually help me formulate our next program topics.

Dr. Barry Singer:

"Taming stress," that's an interesting topic. Taming the stress.

Kyle Pinion:

Absolutely, and with 192 folks I can see everybody, oh the results are pouring in! This is very good, we're gonna get a really great turnout. I'm going to give it a few more seconds. Here we go!

Dr. Barry Singer:

We'll see if sex wins.

Kyle Pinion:

Right now, it is not I'm sad to say. It's a tricky subject, I understand. Well, I think I'm gonna end the polling here and let's share the results. It looks like "complimentary therapies" are things most people are interested in! With "taming stress" second and "exercise routines/adapted exercise" oh, so that's second with "taming stress" third. So that's very interesting stuff. All right, that's something we'll have to talk about, let's talk about soon.

Now, thank you, Dr. Singer. We really appreciate the presentation and kind of diving in to a lot of these different topics. What we're going to do now, is hop into some of our audience questions, which I'm going to go pouring through. We've seen so many good ones, but I want to start with what I think is the most important one of them all. With 2021 to 2022 being Coach K's last year, exactly how far will Duke go?

Dr. Barry Singer:

All the way! He's got one more for Coach K! Yeah, he's been around for a long time. In fact, I was at college at Duke, he was there. So, you know, he's been around for a long time. It's sad to see him move on, but he's had a wonderful, amazing career.

Kyle Pinion:

Well, that was a question from the fine MS specialist out of Santa Monica, Dr. Andy Woo, your fellow board member. I had to share.

Dr. Barry Singer:

That sounds like a Dr. Woo question!

Kyle Pinion:

There we go. I'm a Georgia Tech fan myself. So moving on, can you touch on recommended therapies for people over 60? Are there different recommendations for this demographic, such as discontinuing therapy at a certain age and any potential increased risk of cancer?

Dr. Barry Singer:

I think it's really important. Many of our clinical trials have been studied in people under 55. A lot of the relapsing trials have been in patients 55, I think I mentioned, one with EXPAND trial

looking at the age went up to 60. But most of the trials looked at younger patients. That said, once the drugs get approved there's a lot of real world clinical trials. We look at patients much older, so we start to get some experience once they get on the market. You know, one of the things as you age is called immunosenescence, and so as you age, your immune system is not as robust. So, it makes you at a little more an increased risk for infections. As you age increase risk of malignancies, cancers. We do have to look at the medication. Some medications are safer and have less risk of serious infections like PML, like fungal meningitis. Some of these drugs have higher risk, and some drugs are associated with potential increased cancer risk, at least in the prescribing information. We kind of look at that, and I think it is important to make that decision.

There is a trial going on, it's called the DISCO trial. It's actually looking at treatment discontinuation inside the University of Colorado – is where it started up with John Corboy – and it's looking at could you take people off drugs. Actually I think it started like age 55 and up, so it started pretty young. I think you have to kind of have an individualized discussion with your doctor, is it worth discontinuing meds. I tend to keep them going. It's kind of like an insurance policy for me. I've seen relapses as high as people 80 years old and at least one patient had very active relapse with new activity at age 80. You never know when the disease is over, so it is important to have a conversation with your providers. Am I right for treatment? Should I continue treatment? I think the cost thing is going to be better, because we've now started to hit some generic medications, so I think it'll be easier for some people – out of pocket cost – as they age.

Kyle Pinion:

On the same subject, similar anyway, are there clinical trials available for older adults living with MS to volunteer to participate in, and where can those resources be found? I think I may know the answer that question.

Dr. Barry Singer:

Yeah, so clinicaltrials.gov is definitely the place to go. You can find, search all the clinical trials, and you can search by different ways. The other places, like if you're going to an MS center, you could also contact them and ask them what's available, you know do I fit any profiles, and is this appropriate for me? I think it's that there's definitely room for recruitment, and clearly we need to look at all groups of patients. There's some pediatric clinical trials that have been done now, as well. Because most of the trials were 18 above, so pediatric trials are getting done. But we do need more trials in older patients.

Kyle Pinion:

I just want to make a quick plug, by the way. If you visit the clinical trials section on our website, for everybody listening, we have a tool on there that was created with Antidote for an MS clinical trials finder, and you'll be able to plug in all your information, and you'll be able to find all the information in terms of clinical trials in your area. So check that out! It's a little more fun to look at probably, than clinicaltrials.gov.

Dr. Barry Singer:

It's probably easier to navigate. Yeah, so check out MSAA's website.

Kyle Pinion:

I highly recommend it. So do you have suggestions on natural medicine options for things like fatigue and depression, that are complementary to my disease-modifying therapy?

Dr. Barry Singer:

For fatigue and depression, that's tough. There isn't really herbal supplements that are really, at least proven as far as I know, proven to prevent depression or help with depression. Fatigue, probably the most natural one is caffeine. A lot of people stick with coffee, green tea. The only downside is you got bladder problems, and you've got bladder urgency, so the bladder gets overactive with caffeine. It's going to be a double-edged sword. Unfortunately, I wish there was something that would help. I mean light therapy can help with depression, so that would be something that would be non-supplement. It's tough. I think one of the things that, you know, supplements can make a lot of claims because they're not held to the same regulatory pathway as, you know, with the FDA. It's easy to kind of make claims about what these supplements do. But it is important to sit down, talk to your doc about if you want to start any supplements, and they can let you know, this may be fine to try, or this is concerning and may interact with something.

Kyle Pinion:

Okay this is the big topic that sort of dominated everyone's lives for the last year and a half. Can you share guidance that you might give to your patients living with MS on navigating the pandemic and COVID-19 vaccines, and talk about the general potential side effects from the vaccinations?

Dr. Barry Singer:

Excellent question. I don't know if this is a two second question, but the bottom line is get vaccinated. The vast majority of my patients have been vaccinated, but you know some days everyone's been vaccinated, some days I have a few people that have not. I think at this point in the pandemic, we have not seen an increase in relapses with our patients with MS and we have not seen problems with our patients with MS. I know at our center we've had over 200 people get COVID, though. It's been quite serious for quite a few people. In fact, I think it's really important that you talk to your provider about getting a vaccine.

Really the only people that wouldn't get vaccinated at this point, are someone that has severe allergic reaction to previous vaccines. There's really not a reason not to get vaccinated at this point. We know the Delta variant's spreading like wildfire. In Missouri we're actually number one, we keep flipping with Arkansas as number one and number two, in number of new cases. I'm still having unvaccinated people get COVID. We've seen very few, I've had three patients, that have gotten COVID after vaccination. They were all mild and they called us. We also have an option of antibody therapy, they can, that's an antibody that's infused if you have mild early COVID, and you're outpatient, you can get it infused. It is important to contact your provider if you do develop symptoms of COVID.

But get vaccinated. You don't want to take chances, and if your family hasn't been vaccinated, get them in. Generally, for my patients, I recommend the mRNA vaccine because it's 95 percent effective we know, and some of our MS meds may bring down the power of that.

Kyle Pinion:

Wonderful, well and I will just say, that the MS Coalition has put out a consensus statement around these vaccines that echoed much of what Dr. Singer has said here – really all of it. We certainly would urge you to check that out as well viewers, and I will have my wonderful assistant Alexis, who has been helping me behind the scenes and putting links into our chat

box, she'll be sure to link that in there as well for you to be able to easily access before the program ends tonight.

Last question. This is it before we wrap things up. What is the current outlook in terms of stem-cell research holding any potential promise for breakthrough treatments in MS? What are your thoughts on aHSCT?

Dr. Barry Singer:

All right, so great question. There has been autologous hematopoietic stem-cell transplant, which is basically taking out stem cells, out of the bone marrow, you give someone chemo, and then you re-inject them. It's kind of rebooting the immune system. It's been around for a while, in the world of MS and there's been centers all over. Northwestern was doing it, Ottawa, and then across the globe, you know, from Mexico, to Russia. All over, there are sites that have been doing this. In general, the results have been very positive. So if you look at the patients that, they've gotten a transplant, they've had very low – we talked about No Evidence of Disease Activity – so a lot of these patients have been doing very well. Over time though, some patients do break through and so they start to have new activity. So it's not necessarily a cure for everybody, but for a lot of people, do quite well.

The big question is, now we have a lot more highly effective treatment. There's a trial going on called BEAT-MS and so this is looking at the best available therapy versus a stem-cell transplant. So, kind of seeing how does this really work and do people with a stem-cell transplant, if they really do much better, then maybe that paradigm might change. Generally, most sites do very well, but there have been some deaths – if you pull some of the data together at some sites – some sites a lot safer than others. You have to be real careful you know in terms of site selection, if you go to do this.

The other type of stem cells are mesenchymal stem cells – so you can take these out of the fat, out of blood and then you can inject them. There has been one good study that's been done in Israel looking at giving them in the spinal fluid, and giving them in the vein, and did have some positive results there in a small study, well-designed study. Other studies have not been done great, so you have to kind of be careful of that. I think sometimes people charge you 10 grand to take some out of your fat and then inject it. I've had patients get it and nothing's changed. I think we definitely need more data, but there is some interesting data coming out of Israel on that front. I think our minds have to be open to see what's going to be highly effective, and kind of look at the risk and the benefit for an individual person.

Kyle Pinion:

Outstanding! Well, we're one minute past the hour, and I promised everybody I would let them out at 9:00 Eastern. So that concludes, officially, tonight's webinar. I would really just absolutely once again like to thank Dr. Barry Singer for his enlightening and eye-opening insights into the MS landscape. Dr. Singer thank you so very much for this amazing talk!

Dr. Barry Singer:

All right! Thanks Kyle, I appreciate it and you know MSAA is a phenomenal organization so if you haven't had time go on mysaa.org, surf around, look at all the different resources available to you if you're living with MS, including free MRIs for patients that qualify – trying to get diagnosed or having MS – so check out those resources. They really have a phenomenal array of tools for you to use.

Kyle Pinion:

Thank you, sir! As mentioned, tonight's webinar will be archived to our website. We ask that you take a very brief survey, that's coming up next may already be in our browser – we're gonna link to it in the chat box here before you go. We'd love to get your thoughts on tonight's topics, as well as something you might want to see in the future. Please note that we'll be holding programs like this every month for the next few months, so be on the lookout to MSAA's calendar for programs you will find very interesting and exciting. On behalf of MSAA and Dr. Singer, we thank you so much for joining us. Have a great night everybody! Bye bye.

Dr. Barry Singer:

Bye everybody! Enjoy your summer.