

Siegel Rare Neuroimmune Association 'Ask the Expert' Podcast Series
Fatigue and Rare Neuroimmune Disorders

The audio of this podcast is available at https://youtu.be/-wwt_D7oVKo.

GG deFiebre: Hello everyone and welcome to the SRNA Ask the Expert Podcast series. Today's podcast is entitled Fatigue and Rare Neuroimmune Disorders. My name is GG deFiebre and I will be moderating this podcast along with Julia Lefelar.

Julia Lefelar: Yes. Hi. Hello everyone. I just wanted to say that my name is Julia Lefelar and I am a co-founder of the MOG Project at the SRNA. The MOG Project was founded by myself, my daughter Kristina Lefelar, Amy Ednie and Cynthia Albright. The MOG Project is devoted to raising awareness, advancing research and providing support and advocacy for our community in hopes of finding a cure. I was diagnosed with MOG antibody disease in 2017, but my journey started 19 years ago with a mild vision darkening and a two year bout of debilitating chronic fatigue that thankfully has since resolved. This is what motivated me to explore fatigue in rare neuroimmune disorders. I'd like to thank the SRNA, the doctors and our MOG Project members, Peter Fontanez and Andrea Mitchell for their contributions to this podcast.

GG deFiebre: Great. Thank you so much. And just, just to start, the Siegel Rare Neuroimmune Association is a nonprofit focused on support, education and research of rare neuroimmune disorders. You can learn more about us on our website at, wearesrna.org. This podcast is being recorded and will be made available on our website and for download via iTunes. During the call, if you have any additional questions, you can send a message through the chat option that's available through GoToWebinar. We also want to thank the sponsors of this month's podcast: Alexion pharmaceuticals, Viela Bio and Genentech. Alexion is a global biopharmaceutical company focused on serving patients with severe and rare disorders through the innovation, development and commercialization of life-transforming therapeutic products. Their goal is to deliver medical breakthroughs where none currently exist, and they are committed to ensuring that patient perspective and community engagement is always at the forefront of their work.

GG deFiebre: Viela Bio is dedicated to the development and commercialization of novel life-changing medicines for patients with a wide range of autoimmune and severe inflammatory diseases. Their team is comprised of passionate, talented, world-class leaders with diverse experience in the autoimmune disease space, and their research focuses on well-established critical biological pathways shared across multiple indications. And then also, founded more than 40 years ago. Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes medicines to treat patients with serious and life threatening medical conditions. The company a member of the Roche group has headquarters in South San Francisco, California. For additional information about the company, please visit gene.com. For today's podcast. we are pleased to be joined by Dr. Carlos Pardo and Dr. Bardia Nourbakhsh.

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Julia Lefelar: Dr. Pardo is an Associate Professor of Neurology and Neuropathology at Johns Hopkins University School of Medicine in Baltimore, Maryland. He is the principal investigator of the Neuroimmunopathology Laboratory, member of the HIV Neurosciences Research Group and clinical neurologist at the Multiple Sclerosis and Transverse Myelitis Centers at Johns Hopkins Hospital. His clinical specialization is on neuroimmunological and infectious disorders of the nervous system with particular focus on multiple sclerosis, transverse myelitis, neurosarcoidosis and neurological complications of autoimmune disorders.

GG deFiebre: Thank you. Dr. Nourbakhsh is an Assistant Professor of Neurology at Johns Hopkins University School of Medicine. He is board certified in neurology by the American Board of Psychiatry and Neurology. Dr. Nourbakhsh has an expertise in multiple sclerosis and neuroimmunology. He earned his medical degree from Tehran University's School of Medical Sciences and completed a residency in neurology at University of Texas Southwestern Medical Center. He studied epidemiology, study design and biostatistics, obtaining a Master's of Advanced Studies degree in clinical research from the University of California San Francisco School of Medicine where he also completed a fellowship in MS and neuroimmunology. His research training focused on the design and execution of clinical trials and use of biomarkers in MS. His current research interests include the comparative effectiveness studies of symptomatic and disease-modifying therapies in MS as well as identifying new pathophysiologic mechanisms and therapeutic targets for MS related fatigue. Dr. Nourbakhsh is the principal investigator of a two-center, randomized double-blind crossover clinical trial funded by the Patient-Centered Outcomes Research Institute, which focuses on commonly used fatigue medications for MS. Welcome and thank you both so much for joining us today.

Dr. Pardo: Thank you GG. Thank you.

Dr. Nourbakhsh: Thank you for having me.

GG deFiebre: Thank you.

GG deFiebre: So to start, just to, you know, get a kind of general overview about the potential causes of fatigue in these conditions. You know, what are the main causes of fatigue in neuroimmune conditions specifically?

Dr. Nourbakhsh: Should I go first?

GG deFiebre: Sure. Go ahead.

Dr. Nourbakhsh: Yep sure. So first of all, before talking about causes of fatigue, I want to define what you are talking about, what you call fatigue in neurological or neuroimmune disorder. So, there are many different perceptions of what fatigue is, but mostly today we are going to talk about fatigue as defined by subjective lack of physical or mental energy that is perceived by the patient or

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caregiver to the degree that interferes with the usual and desired activities. So it's important to acknowledge that this is a subjective feeling and it's really, really difficult to measure it by objective measures that we have for other conditions in medicine. So, when we define fatigue by that, it's good to also categorize fatigue again in neuroimmune conditions in neurology. I would like to categorize fatigue as primary fatigue, which means that it's part of the disease. It's one of the essential components of the disease. For example, in MS, fatigue is truly one of the main symptoms of the disease. There is secondary fatigue that is caused by other issues that is seen in neuroimmune disorders. For example, many patients who have neuroimmune disorders, they suffer from bladder dysfunction that keeps them up at night, or they suffer from spasms, leg spasms, that wakes them up at night. And these conditions basically cause fatigue. There is probably another cause of fatigue that may not be directly related to these diseases. For example, many patients who have, uh, neuroimmune disorders may have, uh, thyroid problems, hypothyroidism or anemia. They are comorbid conditions that can cause fatigue. So as you see, we deal with a pretty complex situation here.

Julia Lefelar: Thank you very much for that. You know, just to follow up, how do medical professionals determine what that underlying cause of fatigue that a patient experiences? Dr. Nourbakhsh?

Dr. Nourbakhsh: Sure. So again, like anything else in medicine getting a good history and physical examination is the first step. Just acknowledging fatigue, asking a patient if they have this overwhelming feeling of lack of mental and physical energy. That would be the first step. The next step would be asking about other conditions, comorbid condition, that can cause fatigue. Again, inquiring about patient's sleep, inquiring other medical conditions like anemia, thyroid problems that the patient may be aware of or that can be checked by very easy blood work. So that would be the first step. If we inquire about them, if they are, they don't seem to be a problem, then I assume that this is the primary fatigue that is really a part of the neurological condition that the patient has.

GG deFiebre: Great. Thank you so much for that introduction and explanation. So then, in terms of, is there any sort of relationship between, you know, the amount of time someone has had one of these conditions or their age and you know, how this might affect fatigue frequency or severity? Uh, Dr. Pardo?

Dr. Pardo: So thank you GG for that question. It is extremely important to characterize a couple of concepts that Dr. Bardia outlined in the past few minutes. There are two major categories of fatigue and one is what is described as a mental fatigue and the other one is described as a physical fatigue. You are asking about the age factor and you're asking about duration of the disorder, for example. And these are important factors as well that influence the presence of fatigue. It appears that the age and it appears that the characteristic of the disease are not necessarily major players in defining mental fatigue or physical fatigue. What is important is the magnitude of the neuroimmunological problem and also the

magnitude of the neurological impact of that and the neuroimmunological problem on the body of the patient. Let me give you an example. So in terms of a mental fatigue, one thing that is extremely important to understand is, mental fatigue is that type of situation in which patients feel exhausted, patients feel that they are unable to think very well and unable to concentrate and unable to focus mentally. And many of those elements of fatigue may be related not necessarily with age, but maybe related with the magnitude and extension of the neuroimmunological problem. Let me give you an example. So patients with multiple sclerosis that have a heavy burden of disease in the brain in the cerebral cortex. Those patients may have a higher risk to have more problems in mental connectivity, meaning that the brain networks that are needed to maintain a good and active and an efficient mental level are going to be somewhat affected by the disorder. A different situation may happen in a patient with myelitis. A different situation may happen in patients that have a spinal cord disorder in which, for example, the major burden of the disease is in the neuromuscular system. Because patients with myelitis, for example, have a higher burden of mechanical activity because of the difficulties with mobility. That actually is going to influence mostly the physical fatigue. That physical fatigue is going to be determined not only by the status of neuromuscular function mobility, but the amount of energy consumption that a patient may need for producing effective and efficient movement. So, fatigue is really a complex equation and that is one of the important elements in the which the clinicians that are dealing with all of these disorders need to analyze not only the neuroimmunological problem, but also all the elements in the equation, including the age of the patient, including the type of work, including the type of activity and including other secondary factors. For example, the energy consumption, the diet, weight, and even the sleep pattern that those patients may be experiencing. So that is basically a very complex situation and I tried to outline at least some of the elements of that equation.

Julia Lefelar: Thank you, Dr. Pardo. I want to continue and ask you another question about patients who have relapsing disease. Can the fatigue on its own be an indicator of some kind of relapse or a pseudo-relapse, or even worsening of symptoms for those people?

Dr. Pardo: Unfortunately, fatigue is not necessarily a good indicator. Let me explain why. Fatigue, as I mentioned before, is influenced by too many different factors. And when there are too many different factors influencing the presence of symptoms like a mental fatigue or physical fatigue, it's very difficult to determine if fatigue is going to be used as an indicator of relapse. However, it's very clear that in many neuroimmunological disorders, when there is evidence, or there is activation of neuroinflammatory process, either in the brain or the spinal cord, that is going to determine other problems, particularly their neurological difficulties. So the patient is going to experience and obviously those difficulties are going to magnify symptoms like fatigue. However, to be very simplistic, I think that fatigue is a symptom that reflects the status of a mental and physical neuromuscular function but not necessarily reflects the

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activity of the disease. Many patients that have, for example, a stable immunological activity associated with a MOG-related disorder, so NMO, or even Multiple sclerosis, some of those patients actually may experience regular fatigue and that fatigue may be influenced by other factors like a sleep deprivation or diet. So, again, just to be simplistic, the fatigue as a symptom unfortunately is not necessarily an indicator of disease exacerbation.

GG deFiebre: Great. Thank you. And then, so before we get into the, you know, the different types of fatigue, I know at the beginning, Dr. Nourbakhsh, you talked about how, you know, fatigue can be caused by these various things like not sleeping at night or spasticity. But how, how can someone know whether their fatigue is caused by the disease itself or, you know, for example, some type of depression or something like that? Or are physicians able to tell the difference between those two causes?

Dr. Nourbakhsh: So, you pointed to a very common issue in our clinic. It's as Dr. Pardo also mentioned, fatigue is a very multifactorial issue in these diseases. So it would be extremely difficult to find or pinpoint to a single cause for fatigue. So it's difficult to disentangle someone who has sleeping problem and spasticity and bladder problem and thyroid issues, if they are the only causes of fatigue or truly the disease, the underlying disease is contributing. So in this situation we try to treat all those comorbid conditions. So if someone has bladder issues, waking her up at night several times, we try to work with urology colleagues to alleviate that. If someone has spasticity or painful spasms at night waking the patient up, we try to alleviate that. If someone has, for example, thyroid issues, of course we try to work with the primary care doctor to treat that. Sometimes we see with treatment of these comorbid conditions, the fatigue improves or goes away. So in that, in those moments you can assume that they were the cause of the fatigue. But in many patients, despite treatment of those comorbid issues, still the patient complains from some residual fatigue. And at that point, you can assume that's the underlying neurological damage and network damage in the brain or spinal cord is contributing to that. So basically we try to treat the treatable parts, and if there is any residual fatigue, we assume that's related to the to the underlying disease, neuroimmune disease.

Julia Lefelar: Thank you. I wanted to ask and move on to talk about the types of fatigue. So, you know, sort of touched on this, but can pain really play a role in chronic fatigue in these diseases?

Dr. Pardo: That's an interesting question. So, going to the initial part of your question, is define fatigue and the classification of fatigue. So pain is a factor. Pain is another symptom that is determined by a problem in either the spinal cord - the nerves - or peripheral organs that are obviously providing a distress signal to the brain and the brain is activated to generate the pain signal. So that means that pain is maybe likely a comorbidity in terms of the equation of fatigue. And pain is frequently a symptom that is associated with fatigue and pain is a symptom that is very frequent in any type of neurological neuromuscular anomaly. The

elements that define pain, in terms of the anatomical presence of the pain is in many ways similar to the target of many neuroimmunological disorders are affecting. For example, the pain depends on the structures in the brain that we call central structures, the pain depends on the spinal cord, pain depends on the nerves, the sensory nerves that are associated with conduction of information between the periphery and the brain, and pain depends on receptors that the sensors of the peripheral nervous system in different organs or in different areas of the body, including the skin. So when there is pain, pain is going to activate the structures in the brain that eventually may have that perception of fatigue. So, fatigue as we mentioned before depends on many factors including central factors and peripheral factors. I will say that pain is broadly a major factor that in turn has magnified many of the elements of fatigue, particularly the perception of fatigue. Pain is going to influence other factors. For example, pain frequently increases depression. Pain frequently increases sleep disorders. Pain reduces physical activities. So that eventually is going to influence fatigue. I will stop here because I think that we should focus on other elements of fatigue in neuroimmunological disorders. And I hope I answered your questions, or at least I explained in a very simplistic way the interaction of fatigue and pain.

GG deFiebre: Yes. Perfect. Thank you so much. So then, you know, there there are, you know, a variety of you know, these rare neuroimmune disorders that, you know, that SRNA works with and, you know, different folks maybe have different experiences with the way they, you know, deal with fatigue or how it affects them. Do individuals with the different disorders under this umbrella experience different types of fatigue? Dr. Pardo?

Dr. Pardo: So the answer is probably not. And let me go back to when I defined, by Dr. Bardia and I defined initially. It is: what is fatigue? So, fatigue basically sits in two major categories. Fatigue is the perception of fatigue, or fatigue is associated with performance of activity. And fatigue actually may be defined as central fatigue and peripheral fatigue. And when we have performance fatigue, that is basically the perception of tiredness, perception of being exhausted. It is that type of fatigue actually is associated with two major components. Either central fatigue or center component. And that is when the neuroimmunological disorder, will define what is the magnitude of involvement. Let me give you an example. Central fatigue depends on all of the networks in the brain or spinal cord that affect it. So, here we have disorders like Neuromyelitis Optica in which most of the damage may be in the spinal cord networks, or we have here MOG-associated disorders in which the networks that are disrupted are permanent in the spinal cord but location in some patients also have other brain structures affected, or even optic nerve affected. Or here we have permanent, like multiple sclerosis, that have multi-location damage in the central nervous system networks. So those are central types of factors that determine variability in the amount of fatigue. So the question is, is there any specific fatigue for any specific disorder? The answer is no. However, all of those specific disorders are going to define the magnitude and the distribution of fatigue, and particularly are affecting what we call the performance because it's going to affect the

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neuromuscular function, the amount of motor weakness, or muscle weakness, or the amount of energy depletion that a patient is going to experience for the amount of mechanical disturbance that a patient may experience with different neuroimmunological disorders. So that actually is, is a very important example that yes, in terms of defining fatigue, there is no fatigue in MS, there is no specific fatigue in NMO, there is no specific fatigue in MOG. However, the magnitude of the overall neuroimmunological problem will define, then, what is going to be the major outcome in fatigue and the type of variability in fatigue that a patient may experience.

Julia Lefelar: Okay. Thank you, Dr. Pardo. I want to ask a question about patients who do not have the relapsing remitting disorder that still feel this intermittent fatigue. Why is that, first of all, and for kids and other people, how can we help schools and work situations understand how to interact with those individuals that where their needs vary over time? Dr. Nourbakhsh?

Dr. Nourbakhsh: Sure. So this is I guess something that depends on just accepting and realizing that fatigue, although it's an invisible symptom, is a major problem and it's a very common problem in patients with neuroimmune diseases. For example, again, most of the research has been done in multiple sclerosis. Different studies have reported between 50 to 90% of patients with MS have fatigue, which makes it the most common symptom of MS. And as Dr. Pardo noted, even those patients who have stable disease, who are not experiencing relapses or progression of the disease, they still complain from this severe and disabling fatigue. So not only fatigue is very common in these neuroimmune disorders, it's actually disabling. So there has been studies showing that fatigue could be as disabling as a walking problem. You know, walking problem is probably the most dreaded complication of many neuroimmune disorders including MS, NMO, MOG, but fatigue actually was at the same place. It was rated at the same place as walking problem as a disabling issue in these neuroimmune disorders. So just acknowledge, this problem being acknowledged by treating neurologist and physicians and being conveyed to the employers and families and significant others that, true that this is not a problem that you can see, but this is as real and as disabling as things that are visible, like walking problem. So, again, I think it's a matter of making people familiar with this issue and accepting and realizing that the importance of fatigue.

GG deFiebre: Thank you. Yep. I think that's very important, especially since it's not as physically obvious as, you know, some of these other symptoms might be. So you talked in the beginning, you did talk a little bit about how, you know, fatigue sometimes might go away over time for some folks. You know, is fatigue, you know, both cognitive and kind of physically related fatigue, in these conditions. Is it expected to ever go away or how does that kind of course change over time? Dr. Nourbakhsh?

Dr. Nourbakhsh: Sure. At least based on my experience, I see fatigue mostly as a chronic problem, although it fluctuates, you know, during the day. For example, most

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patients feel better early in the morning and feel more tired in the afternoon or at night. Or for example, during the summertime, many patients, uh, report more severe fatigue. But I have rarely seen fatigue, someone who has fatigue, after a year or two, be completely free of fatigue. So there are fluctuations, but in the big picture, I don't think fatigue usually would be a symptom that completely goes away. Um, at least in my experience and mostly what I'm talking in patients with multiple sclerosis, at least that's the case.

Julia Lefelar:

Thank you. That's a very insightful, and I want to follow up on this - the comment you made because, I certainly experienced what I'm about to describe in this next question. And I know a lot of other individuals with both MOG and ADEM experience this, but you know, they don't suffer from any physical challenges, you know, other than maybe eye damage and things like that. They don't have depression or insomnia, yet in the past they've undergone these acute attacks and they reported a very, very specific type of fatigue that can only be described as a light switch turning off. After resting for an hour or so they're back to normal, only to repeat this after a few hours. Is fatigue in the absence of any, you know, significant visible damage to the central nervous system recognized by neurologists as a sign of the disease? And if so, what, what do you believe is the cause behind that for these ADEM people, especially because you know, in my case, my fatigue after two years resolved, I haven't felt it since, and that's common with a lot of people I talk to with MOG and ADEM? Dr. Nourbakhsh?

Dr. Nourbakhsh:

Sure. So unfortunately, as opposed to multiple sclerosis that there have been many, many, many countless studies about characteristics of fatigue, the natural history of fatigue, many clinical trials of different interventions and medications for fatigue that has been done in multiple sclerosis. The amount of research that has been done in patients with either ADEM or MOG antibody-associated diseases or NMO are extremely small or non-existent. So actually I tried to look for a study describing fatigue in MOG and I could not find any. There are very few reports of studies on fatigue and ADEM, particularly in children because ADEM as you know, is a disease that is most common in children, as well as neuromyelitis optica. Very, very few papers published in that regard. So, this is, I'm hoping that your advocacy would stimulate and advocate for research basically in this field for patients with MOG antibody disease and ADEM. What I can tell you actually, just doing some research. I saw several articles regarding NMO and fatigue, and very interesting that all of them reported that patients with neuromyelitis optica reported fatigue at the same frequency as patients with MS - about 60, 70, 75% of patients with NMO reported fatigue as compared to about 70% of patients with MS. So I think it's mostly a matter of not having data and not having research in these diseases as opposed to fatigue not being a problem. As you said, you described something that I have not encountered and it's very interesting and I'm hoping that we will have more research in this regard in patients, for example, with MOG and ADEM first about the frequency of fatigue and also the pattern of fatigue that might differ from what we see in MS, which is usually a more chronic problem and as Dr. Pardo

mentioned, usually associated with lesions and damage to different parts of the brain and the spinal cord. So if I want to speculate, I would think that probably immunological mechanisms here are more in play. So, we know from other autoimmune diseases, for example, rheumatoid arthritis, it's a disease that we usually don't expect to have nerve damage or brain damage or spinal cord damage except very extremely rare cases. Those patients also complained from fatigue very, very commonly similar to patients with Sjogren's. This is another autoimmune disease, rheumatological autoimmune disease patients complained from fatigue. Again, probably maybe different pattern as what we see in MS. But again just to summarize what I mentioned, unfortunately we don't have much data and much research for me to be able to comment on fatigue in this very, in this relatively rare neuroimmune disease.

GG deFiebre: Thank you so much. I think that was a really good overview and definitely points to, you know, as you said, the kind of, you know, lack of research specifically about this topic and these groups. So, you know, I agree that that's incredibly important and kind of the next steps in all of this. So I think we talked a lot about kind of the basics of fatigue in these conditions and what the potential causes might be. So if we move on to, you know, how someone can treat issues with fatigue in these conditions and you know what options are available. And you can talk about medication options as well as the non-medication options. So just to start are there any medications or drugs out there that can alleviate fatigue? Dr. Pardo?

Dr. Pardo: Thank you for that question. Before going to the issue of medications, I would like to outline that when we are defining fatigue and patients are complaining about fatigue, the most important role for the clinician and healthcare provider is to identify the factors that are associated with that fatigue. So if we like to target fatigue and treat fatigue, we need to determine first, okay, what is the primary factor that is associated with fatigue? What is the underlying disease process? Is this disease process being controlled efficiently? We can talk about treatment of neuromyelitis optica or an isolated myelitis or optic neuritis or multiple sclerosis. The other thing that actually is important is that the clinician needs to identify if that that disorder is affecting a specific pathway that are going to influence fatigue. And one of those pathways that is actually extremely important is the endocrine pathway. So our brain controls every function in our body and one of those functions that is critical is the endocrinological function. So in the brain, there are specific areas that determine what we call the neurological endocrine function, and that is going to influence the production of hormones, and are going to produce the production of hormones that are very critical not only for alertness, but also for physical and muscle activity. So any type of fatigue, actually the clinician needs to understand if that endocrine function is influenced by the neurological disease. Let me give you an example. There are inflammatory diseases such as neuromyelitis optica or MOG in which areas of the brain, particularly an area of the brain that is called hypothalamus that is the center master of endocrine function may be affected. So in that type of situation, if a patient is complaining about fatigue, and the healthcare

provider identifies that one area that is affected by the disease process is the neuroendocrine network, the healthcare provider needs to provide a very good assessment for that endocrine function and eventually replace for months, and replace things that are deficient, when the disease process is affected that day. The second part is that the clinician needs to identify the secondary factors that influence the development of fatigue. Let me give you an example. We mentioned before sleep disorders. If a sleep disorder is a major problem in a patient with neuromyelitis optica because in the middle of sleep, at night, patients are experiencing a lot of cramps, a lot of spasticity, a lot of pain and it's disrupting the sleep. Obviously, that's a factor that needs to be corrected. So that's when we provide patients with a relaxing medication for night, a medication that helps muscle relaxation to avoid too much cramping at night. So that is eventually going to help patients to sleep better and eventually it's going to treat fatigue. The same situation happens with other abnormalities, let's say frequent urinary activity, an increase in urinary frequency and urinary urgency. If that happens at night, patients are waking up 3, 4 times at night and obviously that sleep disruption is going to be a factor next day for fatigue. So the clinician and the healthcare provider is obligated to control that bladder hyperactivity and in that way help the patients who are involved in deep sleep disruption by frequent urination. So that's another level in which the healthcare provider may help to control fatigue. And there is a parallel that is the identification of comorbidities. Let's say there are problems with depression, there are mood changes associated with the neuroinflammatory disorders. So that is obviously, something that the clinician needs to intervene to modify depression or to modify other types of mood changes. And the same happens with other comorbidities. Another example of that is physical conditioning. There are patients that basically can alleviate fatigue just by improving physical stamina and physical conditioning. So those are the three different levels that a clinician and healthcare provider need to target before committing the patient to a specific treatment for fatigue itself. There are medications that are widely used for treatment of fatigue like Modafinil that is also called Provigil, or Amantadine that also called Symmetrel, or other medications like Methylphenidate that is Ritalin, that are frequently prescribed for treatment of fatigue. But it is a major mistake that healthcare providers prescribe these medications without examining very carefully the factors that influence fatigue. I frequently emphasize to my patients, I don't want to prescribe these medications until we are ensured that your sleep deprivation problem is improved or until your bladder dysfunction problem is improved or until other issues related with pain at night or urination at night are improved. Because otherwise, it's going to be really not necessarily a good approach providing a lot of medications for fatigue when other factors are basically ignored. So that is, I'm going to stop here because probably Dr. Bardia may have a lot of additions to my answer, but that is basically the approach that I think that we should follow as healthcare providers with patients with neuroimmunological disorders complaining about fatigue.

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Julia Lefelar: Thank you, Dr. Pardo. That's very informative. I'd like to direct this question then to Dr. Nourbakhsh. So are there any preventive measures that one can take to avoid the fatigue in the first place?

Dr. Nourbakhsh: The easy answer I would say, there is nothing scientifically proven that prevents fatigue. But I want to reiterate what Dr. Pardo mentioned that I also agree that the first step for treatment or prevention of fatigue should not be medications. Not only, we need to try to find other of those secondary causes of fatigue, like Dr. Pardo mentioned bladder and sleep issues. We also, too, we also need to make sure that the patient is not the condition. So actually one of the treatments of fatigue, again usually give my examples from the field of multiple sclerosis because most of the research has been done in that field. One of the interventions that has been shown actually more conclusively than any other medication working for fatigue is what is called graded exercise. So you may think that this is a counter intuitive recommendation. Patients who feel fatigue, particularly physical fatigue, why they should do exercise and workout that may actually worsen their fatigue for the rest of the day. And that might be true to some extent. But if they do what has been studied and has been called graded exercise, meaning they start with very mild, very doable, very short period of any type of exercise, would it be aerobic exercise or weight lifting or stretching or yoga or swimming, and over time, over weeks or months, gradually increasing the intensity of the exercise. So if they could run for three minutes after two weeks, increase it to five minutes, after another two weeks to seven minutes. So I'm just using that as an example. Or if they could comfortably lift two pounds after few weeks, increasing it to three, increasing it to five after a few weeks. And this graded exercise has been shown in randomized controlled trials, which are all golden standards for showing that something works, works in medicine to improve fatigue in MS. So, that has been studied as a treatment, but I assume that probably as preventive measures that could work. If you increase your capacity of doing more and more physical activity over time, that can have a therapeutic effects for sure. And as I said, I can extend that probably to a preventive measure for fatigue.

GG deFiebre: Great. Thank you so much. And then, Dr. Pardo, just a quick question about, you know, the, the fact that many of these relapsing disorders require preventive medicines like CellCept, Rituxin, IVIG, or you know, other medications that are used for acute attacks, like, you know, steroids, IV steroids. What are the effects of these types of preventive medicines on fatigue and then how, you know, how does someone manage their fatigue while taking them? Dr. Pardo?

Dr. Pardo: It's a very interesting question. I'm probably, I will start with the easy one, and it is the use of IV steroids or even oral steroid treatments. Steroids actually act like hormones in our body. Frequently, patients during exacerbation of a neuroimmunological disorder are prescribed with a medication such as IV prednisolone or oral prednisone. And, the majority of patients is somewhat beneficial to control fatigue and many patients actually will report very quickly this was the magic treatment for my fatigue. It's a very interesting

phenomenology and as I mentioned before, it's mostly because the steroids have a hormonal effect on the body and activate many endocrine pathways and metabolic pathways, and patients feel a lot of energy. There is a small subset of patients that actually have the opposite. There is a small percentage of patients that don't react in that way with the IV steroid treatment. And again, going to be actually in a more difficult situation and even experiencing a lot of side effects. That effect that is the hormonal effect from the steroid treatment is transitory and it's not sustainable and, and that's one of the reasons provided for prolonged use of steroids. Yeah, it's interesting and may provide some benefits for fatigue, but it's not sustainable therapy cause produce a lot of comorbidities and a lot of side-effects. Now, the second part of the question is more difficult. What happens with different therapies like Rituxan or Mycophenolate and the effect on fatigue? I don't believe that there is an answer for that, and I believe that those are mostly long-term effects that I'm not sure, I don't believe that there is a good study that demonstrates if those treatments are affecting fatigue. Eventually, theoretically we can say that they affect fatigue because they are controlling the primary disease process and reducing the amount of inflammation in the brain and eventually in that way may help to control fatigue. But I don't believe that there is clear, clear understanding of the role of those medications.

Julia Lefelar: Okay. Thank you, Dr. Pardo. I'm going to direct this at Dr. Nourbakhsh. You know, in general, when should a patient start feeling concerned about their fatigue level and, and when do you think they should reach out to their doctor?

Dr. Nourbakhsh: So I don't think there is any specific time or guidelines for that. When the patient, when a patient sees his or her doctor or neurologist, it's always good to talk about the chronic symptoms that they have including fatigue, including depression, including cognitive problems. Also, I think it's a duty of the physician to regularly inquire about these symptoms. So we of course ask about symptoms suggested for relapse, symptoms suggested for the disease progression. We also routinely regularly ask about these chronic and invisible symptoms. And if it's not the physician asking the patient, I think the patient should volunteer this information. And many of my patients, they do. Even before I ask them, I just ask an open-ended question, how are they are doing? And they mention, they mention this problem of fatigue. If they don't, I usually try to specifically ask about fatigue, their energy level, and changes between, for example, this visit and the previous visit, if there has been differences. So, I think anytime and any visit would be a good time, if a patient is concerned that their fatigue is out of the proportion of what they do. So that's important to realize that many healthy people also get fatigue. But the fatigue that is abnormal and pathological in these neuroimmune disorders is the type of fatigue that's out of proportion of what the patient does and is also affecting their life. So when that happens and if the patient thinks that's the low energy they feel both mentally and physically is out of the proportion of what they do and out of the proportion of other people at home or at work who do not have

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that neuroimmune disorder and it's really affecting their lives, they should bring it up with their healthcare provider.

Julia Lefelar: Thank you. Well that's certainly interesting. I mean, I certainly had that experience and you know, I had debilitating fatigue. And when I got to the doctor, I really found that it was, it was very difficult for them. I don't think that they really knew my fatigue level as they saw me sitting there. So I just wondered if there's any real way to accurately measure those fatigue levels while you're visiting your doctor and talking about this with them?

Dr. Nourbakhsh: Sure. So there is, as we talked earlier, fatigue is a subjective feeling. So there is no marker on the blood work or on the MRI or any other specific test that we can do to objectively measure fatigue at this point. But there are many standardized questionnaires that have been developed to measure fatigue both in the clinical setting. For example, when a patient goes to the doctor and during the clinic visit, those questionnaires and surveys can be used. And also in research, for example, to assess the effect of a medication or an intervention on fatigue, we use these questionnaires that have been validated in many different diseases. Some of them are specifically for MS, some for different neurological diseases. So, in the absence of an objective biomarker, we use these patient-reported surveys and questionnaires in the clinic and in research.

GG deFiebre: Great. Thank you. And then, so you know, if chronic fatigue, you know, is a real symptom of these diseases and, you know, neurologists recognize this, and someone's, you know, work or school life is significantly impacted by the symptom of the condition, how can someone, you know, go about getting the appropriate accommodations, either through disability or something like an IEP in a school. How can then their neurologist kind of be involved in getting those necessary accommodations?

Dr. Nourbakhsh: So, as long as the neurologist, the physician realizes that this is a real problem and this is a common problem and this is a disabling problem, there should be no problem with providing documentation that this patient has this specific neuroimmune disease and is suffering from disabling fatigue that may interfere with their job or with their school performance, and they require adequate accommodation. So, I have had several patients who requested letters stating this issue, and I've provided them with the letters. And usually their employers or their schools have been really accommodating with this issue of...
Fortunately, I haven't had any major issue with, with the employers or with the schools understanding and appreciating and doing the necessary accommodations for patients.

Julia Lefelar: Oh, thank you very much. We have a question here from our community. And basically write that you know, fatigue for them can continue to be a difficult symptom to manage cause they have MS. She says, she swims, or he or she says they swim five times a week, eat healthy, and get plenty of rest. However,

fatigue never ceases. Can you please share any new research trials, et cetera that shows some promise for treating fatigue, uh, outside of Modafinil?

Dr. Nourbakhsh:

Sure. So starting from non-medication interventions. Again, aside from that graded exercise that I mentioned, and it seems that this patient is actually following that recommendation of trying to stay fit and active. A non-medical, a non-medication intervention that again has been in multiple clinical trials shown to be effective for reducing fatigue is what you call cognitive behavioral therapy. So, you know, patients who have had mood issues and depression issues might be familiar with this intervention. It's an intervention that is proven to be effective for alleviating depression as good and as efficacious as medications, for example, SSRIs. Cognitive behavioral therapy that is administered by a licensed therapist is quite effective for depression. It's also been shown to be effective in management of, of fatigue. Again what I'm talking about is specific to MS, but I assume that it may apply to other neuroimmune diseases. The problem is many patients may not have access to a therapist and psychotherapist who who are specialized in doing cognitive behavioral therapy. Talking about medications, Dr. Pardo mentioned the list of medication that they commonly use for treatment of fatigue, including Amantadine, including Modafinil, including psychostimulants, such as Ritalin, Vyvanse, Adderall. The problem with them is unfortunately, we really don't know if they work. There have been several studies done in MS with conflicting results and actually for psychostimulants, for for example Adderall, Ritalin, Vyvanse, there has been no study in neuroimmune conditions actually, but we commonly use them and prescribe them. My colleague and I recently finished a large randomized controlled trials of actually testing all of these three groups of medications: Amantadine, Modafinil or Provigil, and Methylphenidate or Ritalin in patients with MS fatigue. The study was completed about ten days ago and we are going to start analyzing the results to find out if any one of these medications is going to be better than placebo in improving fatigue. So the result of this study can inform us if the use of these medications that we commonly use, and of course they can be associated with side effects, is justified in improving fatigue. Hopefully we will know more, we will know the results in a month or two. And I believe that's going to be helpful. I also work on some novel treatments. For example, you may have heard about the medication called Ketamine, which is an old anesthetic and actually a medication that used to be a medication, a drug of abuse. But in the past ten or fifteen years, it was shown that it's extremely effective in improving depression, even in patients who do not respond to other medications. There, there were some studies that suggest that it may be also good and efficacious for fatigue in other conditions, not in neuroimmune conditions. And we recently performed a small, what we call pilot study. Basically in very few patients, we did a randomized controlled trial and the results were promising that even one infusion of ketamine seemed to improve fatigue based on one or two questionnaires that we did. And based on the other questionnaire, it did not. So the results are not completely clear, but the results were promising. And hopefully we will do a larger study to find out if really giving ketamine to patients that, actually it was recently approved, a nasal

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formulation of ketamine was approved for depression, to see if it also has beneficial effects in fatigue.

GG deFiebre: Oh yeah, no, that's, that's very exciting. You know, I've heard of ketamine in depression, so it's, you know, it's interesting to hear, you know, these you know research findings as well. So thank you. And as we close up, I just wanted to ask if there was anything else you wanted to mention that we didn't cover today that you think would be important to mention.

Dr. Nourbakhsh: I think you covered most of the topics that we wanted to talk about. Maybe I reiterate the importance of research. So fatigue is a multifactorial condition and symptom in MS and other neuroimmune conditions. And, the amount of knowledge is really poor and, as you can tell, the availability of treatment is minimal and poor. So we really, really need more research to find out what are the contributing factors to the development of fatigue in MS and other neuroimmune conditions. And also more research into novel treatments for this extremely common and very disabling symptom. Not only, we talked about this being a common condition in MS, it's also present, common, and disabling in other neuroimmune disorders. However, our understanding, our knowledge about fatigue in other neuroimmune disorders including MOG, ADEM, myelitis, neuromyelitis optica is extremely low. So, it's important patients and family members and people who are affected by these disorders to advocate for not only, of course, finding immunotherapies to control relapses and prevent relapses. Also, we need to do more research for these, again, invisible symptoms that are extremely common and disabling. Hopefully we will have more data and more solutions for, for fatigue in the future.

GG deFiebre: Great. Thank you. Yeah, that's a, that's a great point. So thank you so much for your time. We really appreciate it. We got through as many questions as we could, but, you know, hope to continue the conversation in the future. So thank you so much for your time.

Dr. Nourbakhsh: Yeah, thank you for having me.

GG deFiebre: Alright, bye.

Dr. Nourbakhsh: Bye.