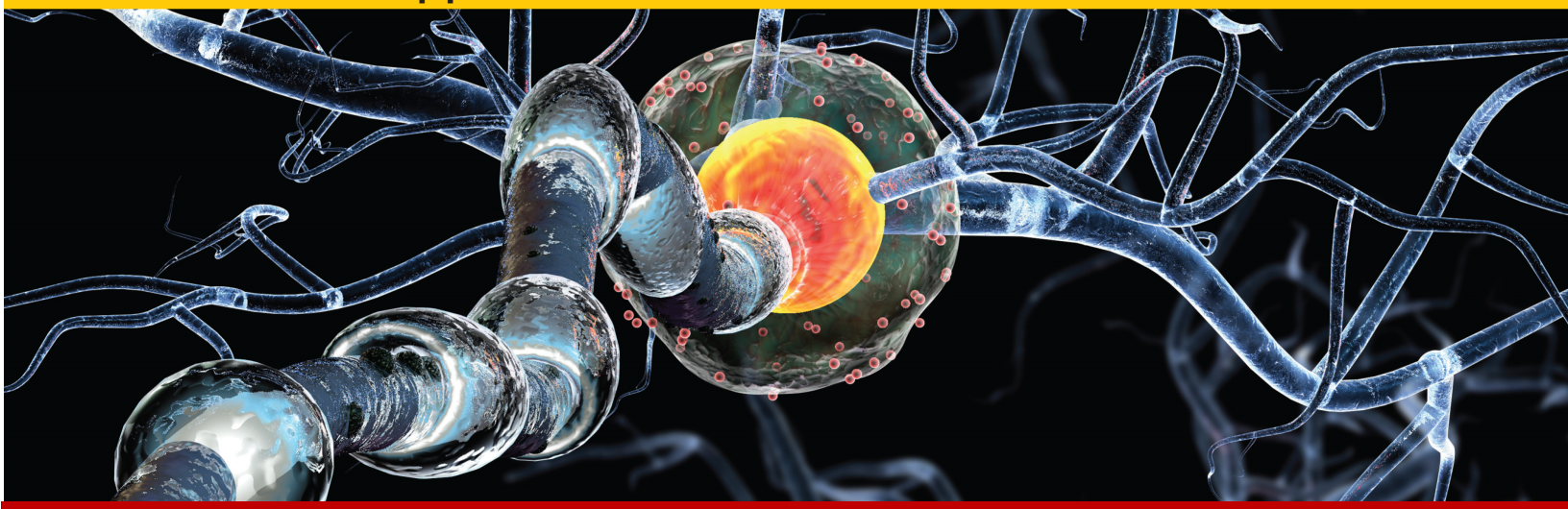
RECOGNITION AND MANAGEMENT OF
MULTIPLE SCLEROSIS

How PAs Can Support Patient Care



CME Available Until February 29, 2024

This activity has been approved for 1.5 AAPA Category 1 CME credits

Contents:

Provided by: AAPA American Academy of PAs

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ACTIVITY OVERVIEW

Multiple sclerosis (MS) is the most common, non-traumatic cause of central nervous system (CNS) disability in adults. In the United States approximately 400,000 people are affected by MS, with approximately 2.5 million affected worldwide. The cause of MS is not known, though it is believed that an environmental trigger initiates an autoimmune event, creating disease in genetically-sensitive people. Women are twice as likely as men to be diagnosed with MS, with most patients presenting with symptoms in their late twenties or early thirties. This educational program is designed to give PAs an overview of MS and to provide much needed education to support the complex management of patients with MS and allow PAs to more effectively collaborate with neurology specialists. Additional training in MS is important for PAs because of their role in health care maintenance and to support patients when MS specialists are not accessible. Through the tactical combination of online and print formats, this program will appeal to various learning styles and allow participants to reinforce their knowledge and acquire new skills that can immediately be applied to clinical practice.

AAPA TAKES RESPONSIBILITY FOR THE CONTENT, QUALITY, AND SCIENTIFIC INTEGRITY OF THIS CME ACTIVITY.

EDUCATIONAL OBJECTIVES

- Recognize the most common neurological signs and symptoms of a clinically isolated syndrome (CIS) that may be encountered in a primary care setting.
- Indicate when neurological symptoms meet the criteria for a MS relapse.
- Use knowledge of treatment-associated risks of disease modifying therapies (DMTs) to provide appropriate preventative care for patients with MS.
- Address comorbid conditions when treating patients with MS.
- Identify patients who may be nonadherent to DMT therapy for MS and refer to treating neurologist when appropriate.

ACCREDITATION STATEMENT

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. The activity is designated for 1.5 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation. Approval is valid through February 29, 2024.

Estimated time to complete this activity: 90 minutes.

HOW TO RECEIVE CREDIT

There are no fees for participating and receiving CME credit for this activity. Participants must: 1) read the educational objectives and faculty disclosures; 2) study the educational materials; 3) complete the post assessments in Learning Central.

In order to receive credit, participants must complete the post-test and evaluation. You will be able to access your certificate of completion in Learning Central as soon as you complete the post-test with a minimum score of 70%. Your certificate will be available under "Transcript" for your records.

DISCLOSURE POLICY STATEMENT

All individuals in a position to control the content of this activity have disclosed their relevant financial relationships with commercial interests. Disclosures from the author(s) are listed below.

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ACTIVITY PLANNERS

John Gentile, Megan Gentile, Joanne Jeffers, and Chris Fischer, Medical Logix, LLC have no financial relationships with ineligible companies during the past 24 months to disclose.

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Michele Hoang, Cheryl Holmes, and Daniel Pace have no financial relationships with ineligible companies during the past 24 months to disclose.

OFF-LABEL/UNAPPROVED PRODUCT(S) DISCUSSION

This program discusses the off-label use of intravenous immunoglobulin.

DISCLAIMER

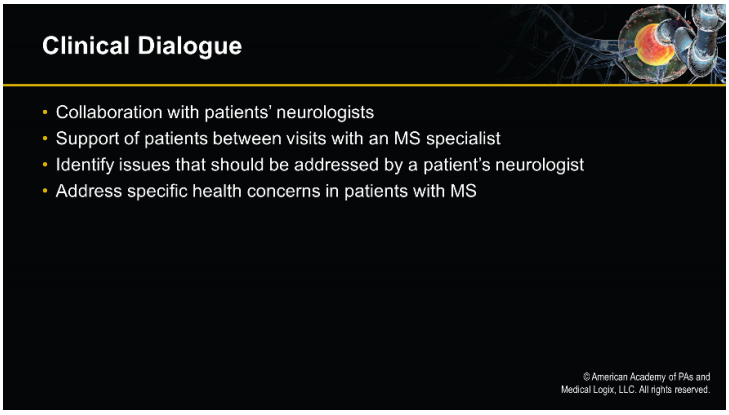
The opinions and comments expressed by faculty and other experts, whose input is included in this program, are their own. This enduring material is produced for educational purposes only. Please review complete prescribing information of specific drugs mentioned in this program including indications, contraindications, warnings, and adverse effects and dosage before administering to patients.

CLINICAL DIALOGUE

Andy Herber, PA: Hello, and welcome to this video *Clinical Dialogue*, "*Recognition and Management of Multiple Sclerosis: How PAs Can Support Patient Care*." I'm Andy Herber. I'm a PA in hospital internal medicine at Mayo Clinic in Rochester, Minnesota. Joining me today is PA Paula Hardeman and Dr. Benjamin Greenberg.

PA Hardeman is a Lead Advanced Practice Provider in the Department of Neurology at the University of Texas-Southwestern in Dallas, Texas. Dr. Greenberg is a Professor of Neurology at the University of Texas-Southwestern in Dallas, Texas, as well. My thanks to both of you for your involvement in this important continuing medical education activity.

This activity is designed to help PAs better understand MS and support the complex management of patients with MS. In this program, we'll talk about how you can collaborate with patients' neurologists, support patients when they cannot readily contact their MS specialist, identify issues that need to be addressed by the patient's neurologist, and address specific health concerns you might encounter in patients with MS.

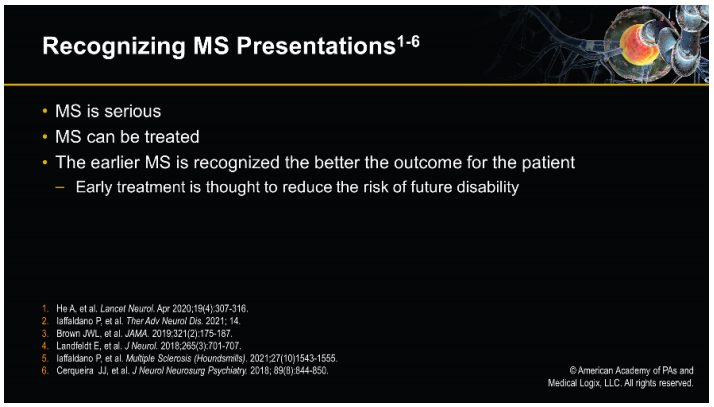


When you complete this course, we'd like you to consider enrolling in the accompanying *eCase Challenge*, where we'll use several case scenarios to apply these topics.

All right. So, Dr. Greenberg, thanks for joining us today. My question to you is, patients show up in the clinic for a myriad of complaints, sometimes weakness, sometimes not feeling well. Why is it important for PAs to know how to recognize those first signs of MS?

Benjamin Greenberg, MD: I really think one of the most difficult jobs in medicine today is being a primary care provider or being on the front lines. Pediatricians, internists, emergency room physicians, advanced practice providers who work in each of those settings see hundreds, thousands of patients a year with a variety of complaints, the overwhelming majority of which are the result of relatively benign conditions that don't need intervention.

But multiple sclerosis is a more serious condition that can be treated, and the earlier we recognize it, the better patients do. And so, we always want our colleagues who are on the front lines to be aware of some of the earliest signs of multiple sclerosis or some of the related diseases so that these patients can get a full evaluation and be diagnosed as accurately, as efficiently as possible so they can get onto a therapy that's meant to reduce the risk of future disability.



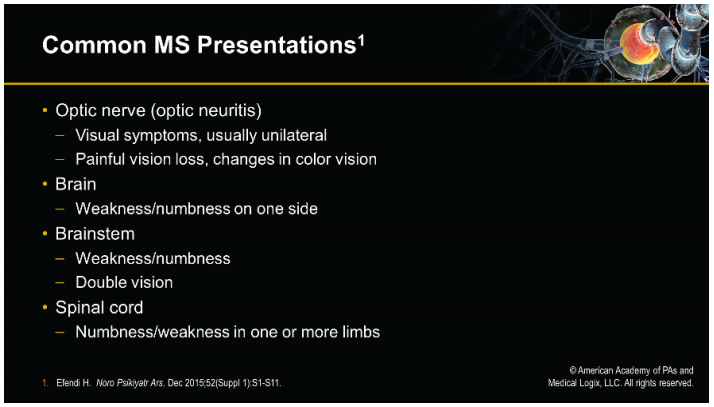
Paula Hardeman, PA: Some of the common presentations primary care could see is, a patient can come in complaining of vision symptoms. And usually, it's going to be in one eye. And so, a patient can come in with a painful vision loss, or they may just experience some changes in their color vision, and this is what's known as optic neuritis. And it's a very classic initial presentation of multiple sclerosis that should warrant the PCP, PA referring the patient to a neurology provider.

Ben, would you like to talk about some other classic presentations?

Benjamin Greenberg: Yes, there are a couple others that you're familiar with, Paula, that can be harder to spot in the primary care setting. So, when we think about the different parts of the nervous system that could be affected, you mentioned the optic nerve, but the brain, brain stem, and spinal cord are the three other places where a patient can have inflammation, they don't know what's going on, and they present to their primary care clinic or to an urgent care center or ER.

When the brain is affected and there are symptoms, patients will have weakness or numbness on one side of their body. When the brainstem is affected, they can have numbness or weakness on one side of their body, and sometimes they can have double vision in association, one of the most common features.

And then finally, one of those common presentations of multiple sclerosis is when the spinal cord is affected. And these patients will present with numbness or weakness in one or more limbs.



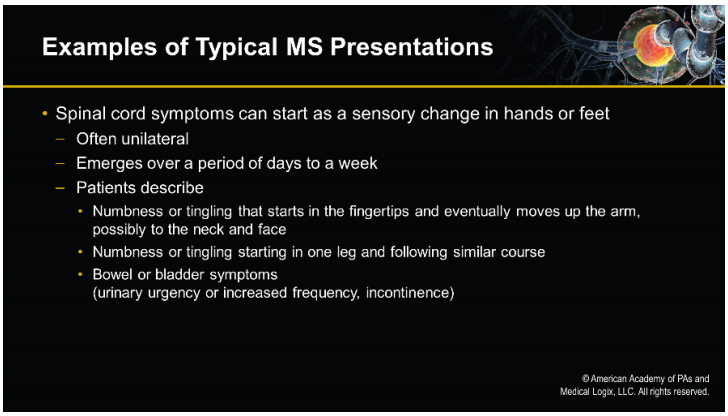
Now, there are some features about the presentations that are important to remember, because, if you think about all the patients who come in with numbness and the majority of those patients have very benign causes, how do you pick out the ones that you should be more concerned about?

So, Paula, when you're talking to your colleagues who are in the front line, and they say, "Well, listen, I get a lot of people coming in with numbness, and they woke up, and their hand was numb, and it went away over a couple hours, do I have to refer all those patients to a neurologist?" you say, "No." But can you give some guidance on what are the features of any of these symptoms that somebody should look for that would prompt that referral and that workup?

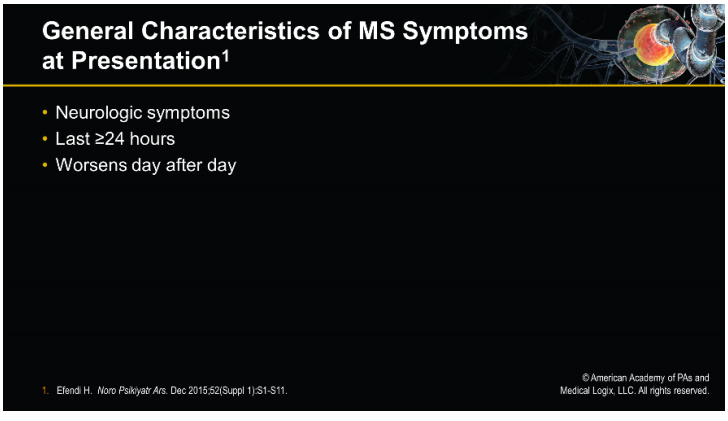
Paula Hardeman: That's a very good point, and you're absolutely correct. So, one of the features that's going to be more relating to the spinal cord is a patient is going to experience some type of sensory changes starting in their hands or their feet. And it's usually going to be on one side of the body, and it's going to be something that's going to manifest over days to maybe a week.

And it'll start with maybe it's just a little bit of numbness and tingling in the fingertips, and it's slowly going to move up the arm, up to the neck, maybe up into the face. That is going to be more signaling something coming from the spinal cord and not something like carpal tunnel or other mild peripheral neuropathies that patients could experience.

The same with the lower extremities. Usually, it will start in one leg and the ascending numbness and tingling. When it's starting in the lower half of the body, other things that patients may come in complaining of is some bowel or bladder symptoms. They may have a urinary urgency, urinary frequency, or can become completely incontinent of bowel and bladder. And so, any of those symptoms with the bowel and bladder would warrant an urgent evaluation by a neurologist or going to the emergency room.



Benjamin Greenberg: Yes. And so embedded in that answer, if you go to the most broad statement of when should you worry about multiple sclerosis and refer for further testing or to a neurologist, it's a neurologic symptom where the symptoms last at least 24 hours and slowly progress beyond that period of time.



So, if a patient comes in and says, "I had a symptom," whether it's blurred vision or numbness or weakness, and it went away on its own in less than 24 hours, much less likely to be multiple sclerosis. But a symptom that lasts more than 24 hours and is getting worse day over day, that's really where the alarm bells need to go off, and a neurologist should get involved in the evaluation.

And, as we've talked about in the beginning, the reason for that early recognition and that referral is to get a patient identified, diagnosed, and on treatment as soon as possible.

Andy Herber: So, guys, is there an age or a gender where we should really start thinking about this, or is there too young or is there a too-old time frame where this is probably not MS?

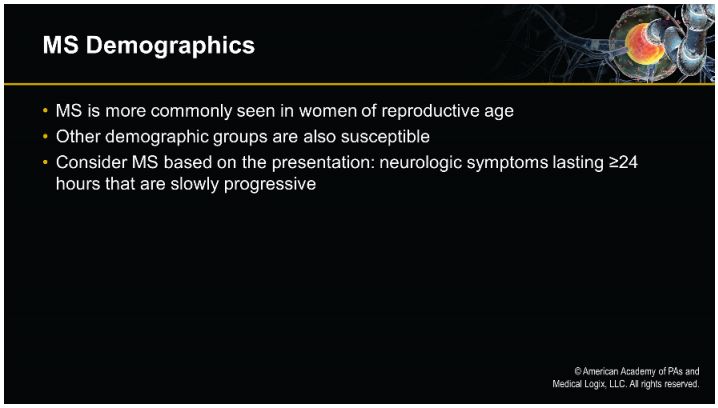
Benjamin Greenberg: So, this is where the demographics can be misleading to us cognitively, and so I want to give the right answer, and then the realistic answer.

So, the right answer on an exam relative to demographics are, women in their later 20s or 30s have the highest rate of new-onset disease. All that sentence says is the highest rate. We have had multiple sclerosis in children as young as 2 or 3 years of age and in adults older than 70 years of age.

So regardless of whether or not somebody fits that key demographic group that has the peak diagnoses, we really need to keep our mind open. I'm reminded of one of the patients I treated who presented to her pediatrician at age 12 or 13 with blurred vision in one eye, pain with eye movements, that optic neuritis syndrome that Paula described so well. And the pediatrician said, "This is stress."

And the mom took the pediatrician aside and said, "Listen, I have multiple sclerosis. I know about optic neuritis. Is there any way my daughter has optic neuritis?" And the pediatrician said, "Children don't get MS." And she lost her vision completely over the next 2 weeks.

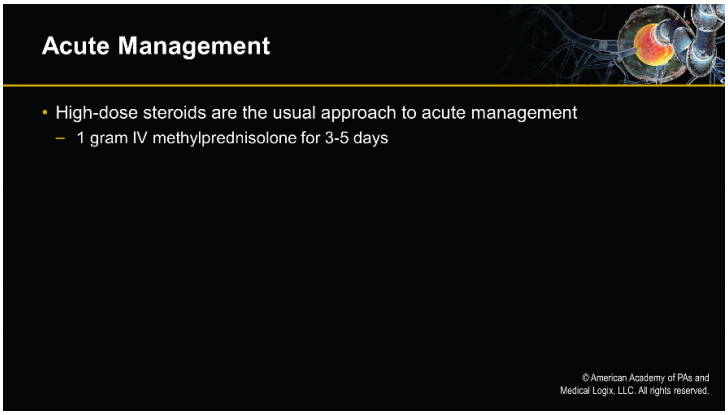
And, so even though that demographic, Andy, you're right, there is a peak group, we need to look for neurologic symptoms lasting more than 24 hours that are slowly progressive, and at least, whether you think it's MS or not, get a neurologist involved to have the conversation.



Andy Herber: I guess my next question is, so, you know, let's just play statistics here. So, you have your 20-year-old female with these optic neuritis symptoms that show up in your office. You're thinking MS. Is there a treatment that you start initially, or do you just say, "Hey, I think you might have this. Here's a neurologist." And if that neurologist appointment not for another couple weeks or months, is there something that you bridge that gap with?

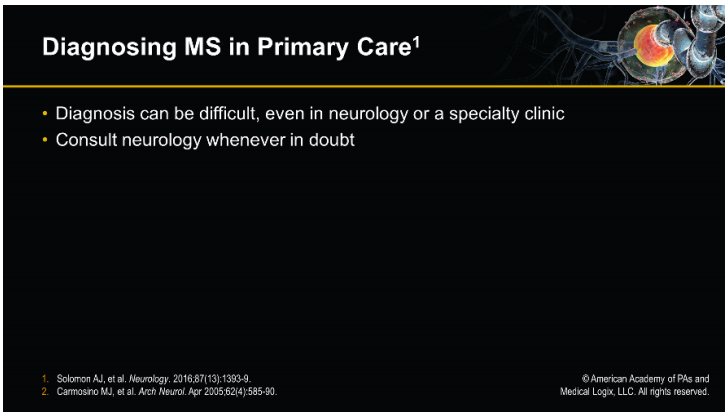
Paula Hardeman: So, if a patient is having acute symptoms and you're concerned that there is something demyelinating that would be consistent with multiple sclerosis, if they're having pretty severe symptoms, it would be well within reason to start high-dose steroids for that patient to start putting out that fire, putting out that inflammation.

So, we typically will treat patients with 1 gram of methylprednisolone via IV for 3 to 5 days, just depending on the severity of their symptoms. And that can at least calm down the immune system for the next 2 to 3 months to allow that patient to be further fully evaluated by a neurologist. Is there anything else you would suggest, Ben?



Benjamin Greenberg: Yes, Paula, I think this gets to be a tough situation. The diagnosis of multiple sclerosis, or, if we zoom out the lens, the diagnosis of inflammation within the optic nerve, brain, or spinal cord, can sometimes be tricky to make. And so, clinicians may have a concern, a suspicion for an inflammatory event of the central nervous system. But even in neurology and a specialty center, we often do testing to confirm it.

And so, if you are not sure, if you have a patient who is having symptoms that raises the concern for multiple sclerosis, but you're not definitive about it, this is one of those times where it's worth it to pick up the phone and call a neurology colleague and move that referral to the top of the list.

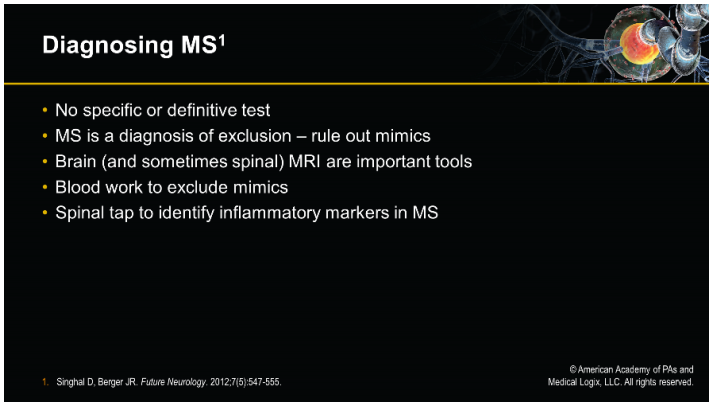


Andy Herber: So, if I get them referred to neurology, is there something that I can prepare them, "Hey, when you get there, you're probably going to have an MRI, or you're probably going to have this battery of blood tests, or they're going to do an EMG?" Are there tests that you guys are going to do that maybe I can prep my patients, kind of let them know what's coming their way?

Paula Hardeman: Now that is a very good question, and you're spot on. So, the technical diagnosis of MS is a diagnosis of exclusion. There is not one specific test that can be done to say, "Yes, you have multiple sclerosis." So, compared to like HIV, you can do a definitive blood test and be able to look at that and tell a person they have HIV.

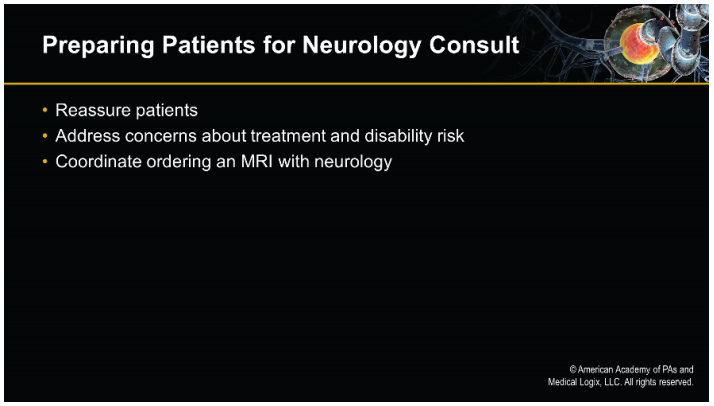
So, for multiple sclerosis, it's basically, what we do is we rule out the mimics. There are a lot of other rare conditions that can cause the neurologic symptoms, the MRI changes and mimic multiple sclerosis. So, you're spot on.

Part of the workup entails doing MRI of brain and C-spine. It also could entail doing some blood work, looking at different rheumatological autoimmune disorders to rule those out. And sometimes, if the presentation or the workup is still inconclusive, the next step would be to do a spinal tap to see if there's any inflammatory markers in the spinal fluid.



Benjamin Greenberg: This is one of those areas where, in the front lines, an advanced practice provider could prepare a patient who's coming in with neurologic symptoms. And you don't want to get out ahead. You want to tell them that, "I have concerns. This could be inflammation. Sometimes inflammation is multiple sclerosis." You want to reassure them that it's a very treatable condition, but that they need to see a specialist.

And if you want to go above and beyond and really make the experience as seamless as possible, that's where that phone call to a neurology practice could be useful, to say, "I'm sending this patient over. Would you like me to go ahead and order the MRI of the brain or of the spine?" such that, when the patient arrives, the testing is already getting going. Those are the collaborative ways neurology and primary care can work together to make the experience as seamless as possible for patients.



Andy Herber: All right, Paula and Dr. Greenberg, we talked a little bit about how someone shows up in the office, and you're concerned about maybe an acute MS, that you would start steroids. We talked about referring to the neurologist. But there's got to be other treatments for MS than just that steroid burst, right?

Paula Hardeman: There are a multitude of different drugs. And so, I believe we may be higher than 23 FDA-approved therapies for multiple sclerosis. So, you have drugs that actually suppress the immune system versus drugs that actually modulate the immune system. There are different drugs that are infusion medications. There are drugs that are injections that can be done at home. And then, of course, we have oral medications.

Benjamin Greenberg: Yes, and the diversity that Paula refers to is continuing to expand. It's even difficult to keep up. And it's been a wonderful experience to have to see the explosion of very effective disease-modifying therapies for multiple sclerosis. The first date back to the 1990s. And in fact, when the first FDA-approved therapy came out, there was a national lottery to see who could get access to it, because there wasn't enough to go around. And so, we've really come a long way.

And so, I think it's important for PAs to understand that multiple sclerosis is a very treatable condition. And I think it's important for that information to be shared with patients, even in the early stages. The moment you say the words "multiple sclerosis" to a patient for the very first time, whether they tell you or not, their mind tends to think about wheelchairs and disability. They think about what they know of the disease, which is really old data, where this was a very disabling condition.

With the variety of therapies, we have now, the overwhelming majority of our patients are put into remission, and our ability to keep people healthy is extraordinarily high. And so, I think it's always important for a PA who's making that referral for a very scary condition to add in, "My understanding is, if this is MS, it's a very treatable condition. Try not to worry too much. We're going to get you to the right place and get evaluated."

Paula Hardeman: That's a very good point. And when I see patients who are newly diagnosed with MS, I like to paint the history of MS. So, as Ben said, the first medication that was FDA-approved for MS was approved in 1993. So, a lot of our history or knowledge of MS predates that.

And if you keep in mind what also happened during that time, MRIs weren't available like they are today. We're able to make the diagnosis of MS sooner, and then we're also able to get patients on drug a lot sooner to prevent the further disability that can occur. It's a very treatable and very manageable disease, and we do not see the progression that we saw 20, 30 years ago.

Benjamin Greenberg: And so, Paula, if I were to ask you about your training around hypertension and diabetes, which you received extensive training in throughout your PA education, the goal was secondary prevention. The goal was starting a therapy to prevent the secondary consequences of that high blood pressure or high blood sugar.

And we taught you that there were responders and non-responders to any intervention. So, there are some diabetics who, despite going on insulin, may still go on to have the complications of diabetes.

I think it's important for us to frame multiple sclerosis the exact same way. What we're doing with our disease-modifying therapies is just secondary prevention. And there are responders and non-responders to each drug. And just like for any intervention for hypertension or diabetes, there may be adverse events associated with some drugs. There may be monitoring needed for some drugs.

Andy Herber: So, you're talking about the diabetes and hypertension, so patients like to know, "What can I expect?" How do we counsel patients newly diagnosed with MS? What's life going to look like to them? How do we explain that to them?

Paula Hardeman: What we see today is that patients are able to go on and live long, fruitful, productive lives. So, I tell patients, "Most patients do not progress. Most patients do not develop additional symptoms. It's more of, the symptoms you have today are usually the symptoms you'll have tomorrow, 5 and 10, 15 years from now."

If patients have problems with neuropathic pain or spasms or muscle tightness, there are different medications that we use in conjunction with the disease-modifying therapy, so, symptomatic management. We have different agents that we can use to help with other symptoms that may have come from their first initial attack.

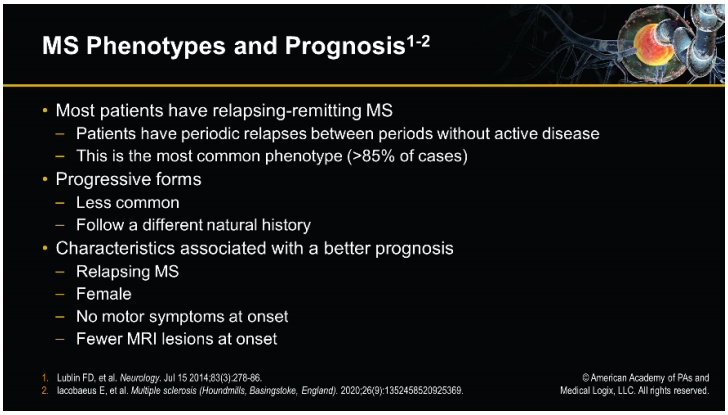
But I really try to reassure patients that having the diagnosis of MS does not mean you have to change your profession, that you can't have children. As we talked about earlier, the high likelihood of an MS patient is a female of childbearing age, and so a lot of females will come and say, "My previous neurologist told me I cannot have children now that I have this diagnosis." And that is not the case. We actually encourage our patients, if that's what they want to have, to have children.

Benjamin Greenberg: I would add two things. And I'll present one and ask you about the other. So one is, it's important to put into context, our conversation so far, Paula, has really focused on the notion of relapsing-remitting multiple sclerosis. And I don't think we'd be doing our job if we didn't just call attention to the fact that there have been these different phenotypes of multiple sclerosis that have been identified over time, and what most PAs and what most primary care clinicians are going to see in the world

is relapsing-remitting multiple sclerosis, so this conversation focuses on that.

There are progressive forms of multiple sclerosis, secondary and primary progressive forms, that have a very different onset and a very different tempo over time. And those needs for those patients are different. And so, when we meet with the patient for the first time, the overwhelming majority are relapsing-remitting,

We can break out our crystal ball and say, "Men do worse than women with this disease. Individuals with motor symptoms at onset have a worse prognosis. People with a big burden of disease on their MRI have a worse prognosis." But all of those prognostic indicators assume a lack of response to therapy.



And for anyone we get into remission, regardless of what their prognosis was, if we get them into remission, they're in remission. And as you say, they're going to remain stable, and they're going to be able to lead their lives the way they want.

I do think in Andy's question there's one interesting topic that's worth discussing, and that is the conversations about overall health and what to expect. I get asked the question all the time, "Is there anything I shouldn't do? Is there anything I should avoid?" And there's a lot of misinformation out there. The most common one is you have to avoid the heat; you can't get overly heated.

And so, when we're talking about kind of a total life care and a 360-degree approach to patient management, Paula, do you have some big-ticket items that you're pushing your patients to do outside of the disease-modifying therapies?

Paula Hardeman: I do. That's a very good point. And so, it's just basic what I call therapeutic lifestyle changes. It's eating a good, balanced diet. So that question comes up very frequently. "Is there a certain diet that I should follow now that I have MS? Should I follow a certain diet to help with my disease process?"

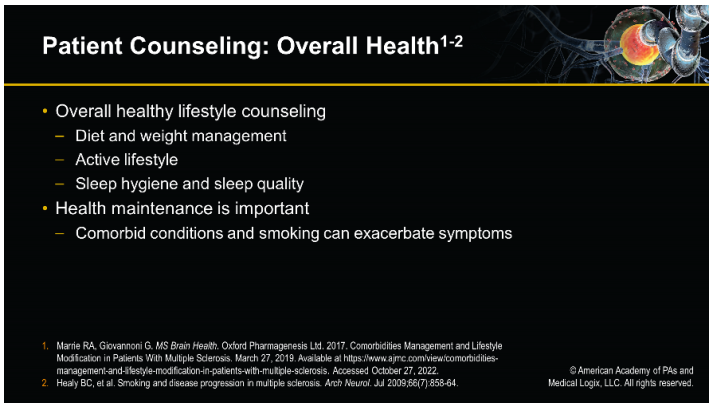
So, the technical answer is no, there's no data to support that you need to be vegetarian or follow these new anti-inflammatory diets where you have to cut out dairy and animal products or different things. But I do encourage my patients to just eat a very good, well-balanced diet.

The other thing that comes up is to stay active. So, whether that means running 2 miles a day or walking 2 miles a day or riding your bike, do whatever you find joy in, and staying active.

And then the other thing that I really emphasize and push on my patients is to get good sleep. And so, I spend a lot of time talking about good sleep hygiene, making sure that they're getting 7 to 9 hours of good-quality sleep and going through those different things.

Benjamin Greenberg: And this is one of those areas that's ripe for partnership between a neurology practice and a PA on the front lines. There are so many things around disease-modifying therapies and MRI and specific tests and labs that we're following in a neurology practice that often the neurologist and the neurology clinic doesn't do as good a job as it should around that overall health and wellness.

And it's important for our MS patients to hear a couple things. One is, just because you have one bad diagnosis doesn't mean you can't get another. And so, we have MS patients who develop heart failure or diabetes. And then the second message is, MS patients with comorbid conditions always do worse.



And so, every investment in overall health and wellness and every gentle push to stop smoking and eat well and exercise and everything you were talking about, Paula, has an even added benefit for our MS patients, because that combination of one of those comorbid conditions and MS really doesn't mix very well.

Andy Herber: We talked about things that the patients can do, but I know as a provider, as a general medicine or hospital medicine provider, if a patient is hospitalized or shows up at a clinic with MS, I'm always worried that I'm going to do something that's going to cause a relapse. If I give this antibiotic, is that going to cause a relapse, if I do this?

So, patients with comorbid conditions are, like you mentioned, are going to get sick or going to need antibiotics. Are there things that we need to be aware of as general providers that we shouldn't do, and maybe that saves you guys a few phone calls?

Benjamin Greenberg: Yes. I want to have fun with Paula on this one. I want to go through our top maybe five calls we get about this. And it's a great question, and we laugh about it because I, you know, when I'm working with a patient with a complex medical condition that I don't focus on, it's a very legitimate question. And we reassure everyone, there's essentially nothing --we'll talk about one exception, that you can do to our patients that will cause harm. But I'll give you our top few that we get.

So, Paula, you get the phone call. A person's having dental work. Do they need special clearance in order to get dental work if they have MS on any of the drugs we use?

Paula Hardeman: They do not need special clearance to get dental work. You can premedicate them with the antibiotic, and anesthesia is perfectly fine for dental work.

Benjamin Greenberg: If they have an infection and need an antibiotic, are there any drugs that people have to avoid prescribing in a patient with MS?

Paula Hardeman: No. Whatever antibiotics, whatever they need to fight that infection is perfectly safe and fine to prescribe.

Benjamin Greenberg: And here is what I think is our number-one phone call we get. "My patient is pregnant and is going to go into labor at some point. Can they have an epidural?"

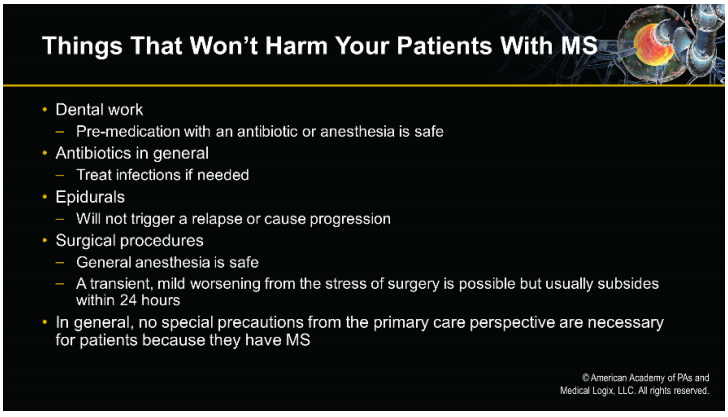
Paula Hardeman: Yes, your patient can have an epidural. Doing an epidural is not going to trigger a relapse. It's not going to cause the MS patient to all of a sudden start progressing. So, if that mom wants to have her epidural, please give it to her.

Benjamin Greenberg: And then our final question we get is around surgery. The patient needs their appendix out, their gallbladder out. They need some sort of surgical procedure. Are there any special precautions we have to take in a patient who needs general anesthesia or surgical intervention who has MS and may be on one of these drugs?

Paula Hardeman: There are no precautions that need to be taken. This question comes up quite frequently, and there's, "Should we hold the medication? Should we not?" There's no need to hold the medication. For my counseling to the patient, what I'll share is the effects of anesthesia. And I think it's the overall stress of the surgery could cause just mild worsening of their symptoms immediately after the surgery.

So, I will educate my patients to say, "Expect mild worsening of your symptoms. It will usually subside within 24 hours. If it does not subside within 24 hours, then let your treating team know and request for a neurologist to come and examine you.

Benjamin Greenberg: So, we had the long answer, Andy. The short answer is, in general there is nothing that a practitioner can do that would harm an MS patient. And I just want to make one edit to that and one comment.



The one exception to this this is when it comes time for vaccinations, which happens in the front line all the time. And in general, the following rules should be followed. Killed vaccines are fine for all of our MS patients. You don't have to think about a killed vaccine or the mRNA COVID vaccines. Any of those are fine.

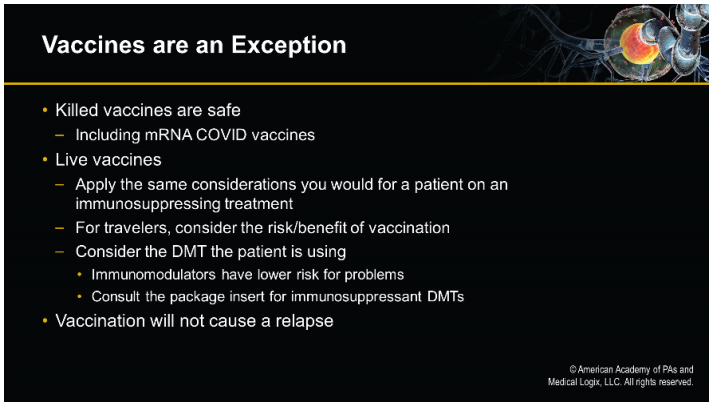
It's when we get into the live vaccines that things change. So, Paula, when you're counseling our patients or our colleagues on the front lines, how do we counsel them? How do you talk to them about screening if somebody needs a live vaccine relative to multiple sclerosis?

Paula Hardeman: Sure. So, part of it also just depends on which vaccine we're referring to. Where I get this frequently is that patients are trying to travel overseas, and they may be going to an area where something may be endemic, say, yellow fever. And then at that point, it's just really a conversation of looking at the risk, looking at where they're going and making that risk-benefit ratio of should they get that vaccine?

In general, if a patient is on an immune-modulating drug, then it would be perfectly safe to do a live vaccine. This gets more concerning if a patient is on a true immunosuppressant drug.

Benjamin Greenberg: And so, embedded in that answer, and just to make sure we make it crystal-clear for our colleagues, we get the question all the time, "Will a vaccine cause a relapse?" And the answer's no. So, the vaccination isn't a risk for relapse.

But to your point, if you're immunosuppressed, just like if you were a transplant patient and immunosuppressed, or a rheumatoid arthritis patient and immunosuppressed, there are risks to live vaccines because of the immunosuppression, not unique to multiple sclerosis. So killed vaccine is fine. Live vaccines depend on which drug you're on. But none of them should induce a relapse.



So, Andy, short of the vaccine issue, there really isn't anything I can think of that a practitioner could do that would harm an MS patient or induce a relapse in an MS patient.

Andy Herber: Paula, earlier you mentioned that if females want to have children that have MS, they should go ahead and have children. Is there any medication that they're on during this MS treatment or any timing or anything that they need to be aware of?

Paula Hardeman: No, great question. So definitely, depending on which disease-modifying therapy, there are some medications that need to be stopped prior to getting pregnant. And so, of course, that needs to be a conversation with a neurologist before planning to even get pregnant to see, do they need to stop it? Some of our medications can cause a rebound effect if it's stopped abruptly and there's not a plan in place to treat with high-dose steroids or something else to prevent a rebound effect.

Once that discussion has been had and a patient is off of their drug if they need to be, it is perfectly fine and safe to get pregnant, like I mentioned earlier. Our patients do well when they're pregnant, and they don't really have relapses. They don't really have increased symptoms. They actually feel pretty good. And I get a lot of moms who just wish they could always stay pregnant for the rest of their life because they do so well.

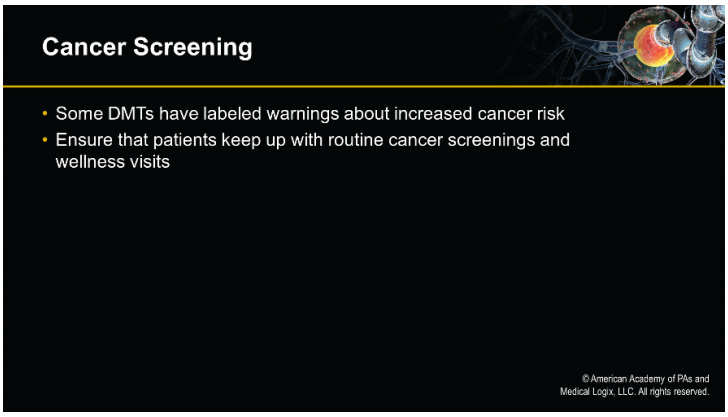
There is a little bit of concern in the postpartum time frame. So, within maybe 2 weeks after delivery, there is a slight increased risk of having a relapse. And we feel this is probably due to just an abrupt change in the hormone levels. When baby is delivered, placenta comes out, and that hormone change that occurs right after delivery.

And so as a result, we tell moms, deliver, and once they get home and baby's safe and they're doing okay, we'll use either IVIG or high doses of steroids to pretreat them to prevent any type of relapse, because it just would be horrible to be home with a new baby, and then all of a sudden you start having a little bit of numbness and tingling in your hand and fearful of having a relapse and everything. Ben, do you do anything differently with your postpartum patients?

Benjamin Greenberg: No, I'm right in line with you. I'm a big believer in a dose of steroid in the week after delivery to give protection for a new mom after delivery against relapse, and agree that pregnancy, labor, delivery, epidurals, everything we've talked about, can proceed exactly the same for one of our patients versus somebody without MS. The issue is really what therapy they're on and knowing which of the therapies in particular we want to avoid pregnancy with.

I will say, whenever we talk about reproductive health and women's health issues relative to multiple sclerosis, we'd be remiss if we didn't talk about some of the issues with some drugs and labels around cancer screening, as well, particularly breast cancer screening.

It's true that for some of the drugs we use, there are specific labels about concerns about increased risk of cancer, breast cancer, sometimes skin cancer. And so, just like we have all women do regular health maintenance with OB/GYNs and primary care physicians and dermatologists if needed, it's true across the board, whether or not somebody is considering having children or not, that they need to keep up with cancer screening and wellness exams.



And so, a lot of these issues, whether it's about pregnancy and delivery or about screening for cancer, are going to be related to which disease-modifying therapy the patient is on, not the diagnosis of multiple sclerosis. So, if you're on the front lines and you're seeing a patient come in with a drug that you don't recognize, you can look it up, you can look at the package insert, or you can simply contact your neurology colleague and say, "Is there anything different I need to do for this patient based on their drug?" And we're always happy to partner up and make sure that we're getting the right monitoring done.

Andy Herber: All right. Thanks, guys. So, you know, we're hopeful that these patients with MS have a smooth course with the disease-modifying therapies. But we need to be prepared for the potential of relapse. And what does that look like, for one, and then, what's the best way to manage that for the PAs in general medicine, either outpatient or in the hospital?

Paula Hardeman: In our world, we look at, is there a pseudo-relapse occurring? Is there something underlying, such as an infection? So, it's very common in our patients to get a urinary tract infection, but this can also occur in any infectious setting, whether it's having influenza, pneumonia, bronchitis, sinusitis, and cellulitis. Any underlying infection can cause a temporary worsening of their symptoms.

And so, their symptoms will manifest the same way they did as that initial presentation. They're going to have worsening of their symptoms that are going to last for 24, 48, 72 hours. And so, one of our screening questions we start to ask, "Well, are you having pain with urination? Are you coughing? Anything that could suggest there's possibly an infection going on?

And if they answer yes to any of those questions, then we'll advise to see their primary care, or to go to urgent care if it's Friday at 4:45, so they can be further evaluated, and then if there is an infection, treat that infection. And once the infection has been treated, their symptoms will start to improve, and they'll go back to what their baseline is.

But suppose they say, "I'm not having any symptoms suggestive of an infection." What their symptoms are going to look like, usually it is a worsening of their old symptoms. But the key thing, what I tell my patients, if they start having any new symptoms that are coming on, again, in that time frame of getting worse over the 24 to 48 hours.

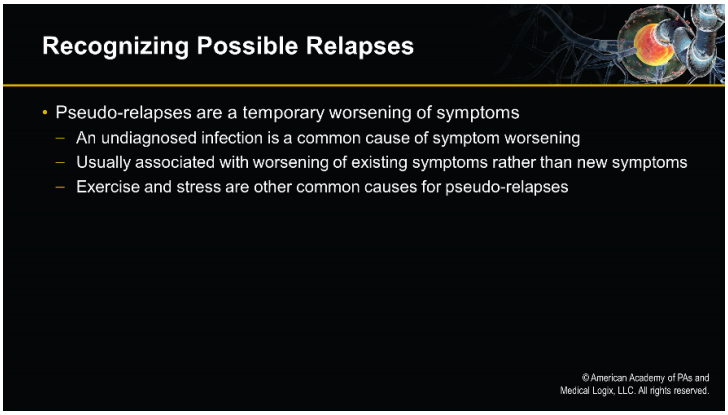
So, if you're accustomed to having numbness and tingling in your leg, and now you start having something in your arm, that would be something to warrant a call to your neurologist, or even if you're going to your PCP, to mention, and do a physical exam to see, is there any differences in the physical exam from previous that could suggest that a person has a new onset of weakness in a certain muscle group, just some type of new sensory change, to start the workup for a potential relapse? Ben, would you like to add something?

Benjamin Greenberg: No, I think you covered everything. And so, my mind works in kind of a checklist pattern, an algorithm pattern. And so, if you have a patient who's contacting you about new symptoms or about symptoms, and you're worried about a relapse, step one is, are these symptoms new or old?

So, as Paula said, if this is someone who's only had sensation symptoms in their legs, and now they come in with blurred vision, and they've never had blurred vision before, that goes to the front of the line for concern of a relapse. If the patient is having worsening of old symptoms, that is much less likely to be a relapse. That's more likely to be this phenomenon called Uhthoff's phenomenon that Paula described in the setting of an infection or a fever, where old symptoms can intensify, and it's not representative of a new attack.

And that's a very important concept. Not all symptoms mean there's a new MS attack. And so, we separate out whether or not somebody's having a true relapse or a pseudo-exacerbation so we can decide with accuracy is their disease-modifying therapy working or not?

If something is deemed to be a relapse, we treat it with steroids. If something is deemed to be an exacerbation of old symptoms due to an infection, we treat the underlying cause, whether it's an infection or anything else.



It's worth noting that Uhthoff's phenomenon, while it most commonly happens with infections, Paula, you and I have seen patients where their symptoms get worse with exercise, their symptoms get worse with stress, and I think we've had at least one patient whose symptoms get worse during arguments with family members. And so there can be lots of triggers for a worsening of symptoms that are completely separate than a new immune-mediated attack on the brain.

Andy Herber: When we talk about relapse, as well, we talked about some of the causes, whether it be infection or things that could mimic that. There's got to be, especially in today's day and age, with cost of medications and how busy people are, what about people that maybe forget to take their medications, or they run out. What does that look like?

Benjamin Greenberg: The issue of adherence is massive. And in our world, I think this is true for every condition. So, if we talk about diabetes, if we talk about hypertension, the topic of adherence is a massive one, because, as our Surgeon General from decades ago said, the medicine doesn't work if you leave it in the medicine cabinet. And the same is true for multiple sclerosis. So, if somebody comes in with a relapse, one of the things we screen for is, are they actually taking their disease-modifying therapy?

What differs in our world is, access to care and access to medication and copays and deductibles cause a real issue for our patients in terms of getting timely and consistent access to the medication they need.

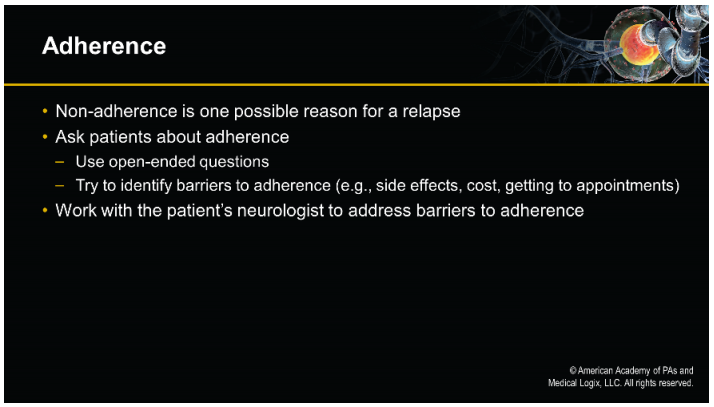
So, it's routine for us to ask open-ended questions. "Do you have any obstacles to accessing or taking your medication? Is there any barrier that's there?" And it's really important for us to partner with our primary care colleagues to be asking the same questions, because I've found over time that sometimes patients are shy to tell me about certain things, but they may have a different relationship with a primary care practitioner or their PA, even their OB/GYN's office or pediatrics office, and they may have a conversation with them that they're not having with me.

And I think it's a great place for us to team up and ask about adherence, because it's a real issue. I mean, Paula, what are your thoughts on this?

Paula Hardeman: No, I would completely agree. And so, I was going to say something a little bit different. I have experience where patients are embarrassed to share certain concerns with you around adherence but will open up more freely to me as the PA, because they feel like I'm going to be nicer to them. But you bring up a good point. They may have a really great relationship with their primary PA, and might share, "You know, taking this medication every month is putting a huge toll on my family."

And so, as you've mentioned earlier in this conversation, to really partner with our primary care colleagues, that would be a great way of just checking in and asking, "Are you still taking your MS medication as prescribed? Are you having any issues, any potential side effects?" anything that could potentially cause the patient to want to stop taking the medication.

And then please, by all means, reach out to us and say, "The patient is concerned about cost. The patient is concerned about access," whatever the underlying issue may be. And there are a lot of different resources that we can help keep patients on medication.



Benjamin Greenberg: Yes, and a great point there, Paula, is often as healthcare providers, we're reluctant to ask a question about something that we wouldn't know how to address. If they tell me they're having side effects, I don't know how to manage it. I need to talk to somebody else. But that really shouldn't be a barrier.

And so, asking on the front lines about side effects from the MS medications, if your patient endorses something, it's fine to say, "Thanks for telling me. I'm going to let your neurologist know and connect you to address that." You don't have to be able to solve the issues, but asking about them shows an interest, shows how important it is and can reinforce that the healthcare team as a whole is trying to promote adherence.

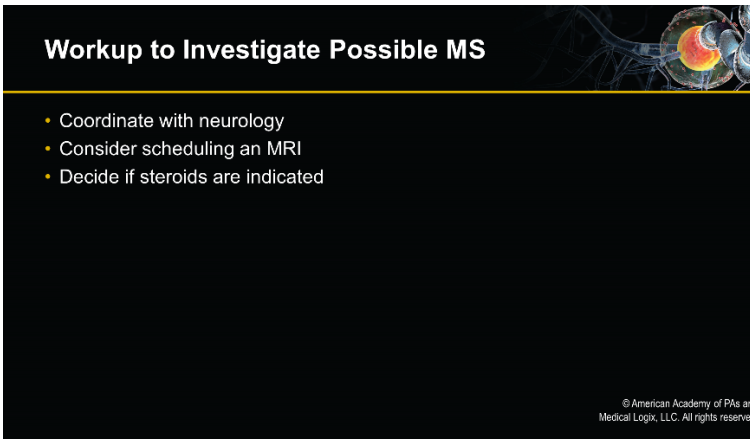
Andy Herber: So, as we come to the end here, as we want to wrap things up, I just had one question that I'm hoping each of you could answer.

So, we have a primary care PA or a hospital medicine, general medicine PA, and we have a patient that shows up with maybe some vision changes and some weakness, and we start thinking MS. What's the perfect, if it went perfect, standard of care, exactly how a neurologist would want it to happen? Can you walk us through and summarize what this perfect workup, treatment plan would look like?

Benjamin Greenberg: So, it's a wonderful question with an "it depends" answer. And the honest is the severity of that symptom.

So, I think it goes without saying, if the vision loss or the motor deficit is so severe that it is interfering with daily activity in any way, that's an emergent care referral. And so, it's perfectly appropriate to get neurology consultations in an ER or in a hospital setting for that situation.

But assuming that it's not that emergent situation, I would say the ideal scenario is the following: a phone call from the office, from the provider to a neurologist, to say, "Hey, Ben, hey, Paula, we have this patient. I'm worried about inflammation. I'm worried about MS. Can they get in to see you quickly? And would it be helpful for me to order the MRI? Would you like me to go ahead and start steroids or not?"



It would kind of be that communication. I think that would be the ideal situation. Paula, would you add or edit any part of that?

Paula Hardeman: No. I would say that would be the perfect situation. If you're having something that's concerning, to reach out and say, "This is what I'm seeing. What should be my next best steps to do for this patient?"

Andy Herber: I'd like to thank both of our expert faculty, PA Hardeman and Dr. Greenberg, for joining me. And I would like to thank you, our audience, for participating in this important continuing medical education activity.

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CLINICAL PEARL

In this *Clinical Dialogue*, we focused on how PAs can assist in the management of patients with MS. Although you would not be asked to diagnose a patient who has had a CIS and possibly MS, we discussed the most common presenting symptoms in the diagnostic workup that patients can expect.

The most important role for a primary care provider is to ensure patients with MS continue to receive routine health care maintenance. Comorbid conditions and lifestyle can exacerbate, worsen or mimic MS symptoms, and it's important to provide an ongoing screening, counseling and treatment for them.

Depending on the DMT a patient is being treated with, you may encounter laboratory abnormalities. When this happens, consult with the package insert for the patient's DMT to see if these abnormalities are an expected therapeutic effect, a possible adverse event or unrelated to the patient's treatment.

Ensure that the recommended cancer screening guidelines are followed, since some DMTs may be associated with a higher malignancy risk.

MS does not affect fertility, and many patients have normal pregnancies and can breastfeed, and pregnant women with MS should consult with an OB/GYN. Ask about reproductive plans and birth control, since some DMTs have a risk of fetal harm.

Patients may come to you with symptoms of a possible relapse. The first thing you need to do is rule out non-MS conditions that are causing the symptoms. If you think the patient is having a relapse, have them contact their neurologist for treatment.

Relapses are often unavoidable but can be precipitated by nonadherence. Ask the patient about missed doses, side effects and other factors that might cause them to miss doses.

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CASE CHALLENGE

Case Presentation 1: Recognizing a Possible Case of MS

Kay is a 22-year-old woman who has had headaches that she describes as a dull ache localized around her right eye every day for about 2 weeks now. The headaches are bad enough (7 on a scale of 10) that she feels her vision, especially in her right eye, is blurry and like she's looking through a haze. Her symptoms seemed to start with blurry vision after a late-night study session, and she woke the next morning with a headache. Her vision is much worse in her right eye than her left (20/200 vs. 20/20). On examination, her eye movements are normal, but the pain intensifies with movement. She is otherwise alert and has no significant medical history. Her vital signs and temperature are normal and she is not currently taking any medications.

Question 1

What is the definition of a clinically isolated syndrome?

- **A.** The basic diagnostic criterion that must be met for a diagnosis of MS
- **B.** The first clinical onset of symptoms that may indicate a patient has MS
- **C.** A single, self-limiting episode of neurologic symptoms that mimics MS
- **D.** Neurologic symptoms that can be correlated with one or more MRI lesions in patients who have MS

The correct answer is B. A clinically isolated syndrome (CIS) is the first clinical onset of symptoms that may indicate a patient has MS.[1] Patients with a CIS exhibit signs of the underlying disease process that causes MS—inflammatory demyelination—but they do not yet meet the diagnostic criteria for MS.[2] In order for a patient with a CIS to meet the criteria for MS, neurologists will look for clinical or MRI signs of previous demyelinating events, or will monitor patients for new signs or symptoms of a demyelinating event.[1,2] While most patients who have a CIS will go on to be diagnosed with MS, this is not always the case. In some studies, more than two-thirds of patients who had a CIS were later diagnosed with MS. The timing of a second neurological event that confirms the MS diagnosis is highly variable and can be delayed by early treatment with a disease modifying therapy (DMT).[3-5]

Question 2

Which of the following presentations is not likely to be associated with a CIS?

- **A.** Neurologic symptoms with a rapid onset or resolution
- **B.** Unilateral visual symptoms
- **C.** Numbness that lasts at least 24 hours
- **D.** Weakness that completely resolves after several days

MS is most common in women in their second through fourth decades, and the first presentation has some typical characteristics that help differentiate it from other possible diagnoses.[1,2,6] The symptoms associated with a CIS are the same as those that would be expected in a patient with MS who is having a relapse, but they occur in a patient who has not been previously diagnosed with MS. A CIS is a monophasic central nervous system (CNS) clinical event. Many patients will present with focal symptoms, but about 20% have a multifocal presentation. Symptoms develop acutely or subacutely, last at least 24 hours and may resolve partially or completely. An important caveat is that infection or causes of encephalopathy should be excluded before suspecting a CIS.

Some neurologic syndromes are common CIS presentations (Table), but many patients' first presentations are optic neuritis, a brainstem or cerebellar syndrome, or transverse myelitis.[1] Patients presenting with a these types of neurologic symptoms that last at least 24 hours should be investigated for possible MS by a neurologist. Therefore, the correct answer is A, since a hyperacute onset of neurologic symptoms could be a sign that the patient's symptoms are not a CIS or MS-related.

In this case, Kay presented with signs typical of MS-related unilateral optic neuritis with an acute onset and duration of at least 24 hours. In the absence of fever or signs of an infection, she should be evaluated by a neurologist. A neurologist will first exclude other possible explanations for her symptoms. Patients with a possible CIS should have a brain MRI with and without gadolinium contrast, and other MRIs may be useful (e.g., cervical and thoracic spine). MRIs should be performed in consultation with a neurologist, but if an urgent referral is not possible, a discussion with a neurologist is helpful.

MS has both spatial and temporal aspects, and part of the neurology work up will be to look for demyelinating events prior to these presenting symptoms.[7] The neurologist will look for signs of existing or prior demyelinating events in characteristic regions of the CNS using a neurologic exam, imaging and Kay's history. It is only after excluding other causes and finding corroborating evidence that MS can be diagnosed, and a common pitfall is overreliance on MRI.[8,9] If clinically significant, active inflammation from MS is suspected, a common initial therapeutic intervention is high dose corticosteroids (1000 mg methylprednisolone or equivalent).

Table 1. Common CIS presenting signs, and red flags that suggest another diagnosis is likely.

Affected System	Red flags suggesting another disease process
Optic nerve • Unilateral optic neuritis or visual loss • Painful eye movements • Afferent pupil defect • Normal disc or retrobulbar swelling	• No pain • Retinal exudates • Retinal hemorrhage • Severe disc swelling
Brainstem • Bilateral internuclear ophthalmoplegia • Multifocal signs • Sixth nerve palsy	• Hyperacute onset • Vascular territory signs • Isolated trigeminal neuralgia
Spinal cord • Partial myelitis • Sensory symptoms • Lhermitte's sign • Deafferented upper limb • Partial Brown-Sequard syndrome	• Hyperacute onset • Complete transverse myelitis • Sharp sensory level • Radicular pain • Areflexia
Cerebral hemisphere • Mild subcortical cognitive impairment • Hemiparesis	

Case Presentation 2: Preventative Healthcare Appointment for a Patient with Relapsing MS

Allontae is a 57-year-old African American woman who has been seen at this practice for several years. At the age of 31, she was diagnosed with MS and regularly meets with a neurologist. Allontae is a mother and grandmother, married, and manages a small retail salesforce. She started treatment with an interferon several years after being diagnosed and has changed DMTs several times as new ones have become available, or as she's needed to for efficacy or to reduce side effects.

A relapse 5 years ago affected her mobility, and now she uses a cane and a brace to walk even short distances. She is also partially blind in her right eye. In the past, she has mentioned that MS has caused upper and lower extremity sensory symptoms (numbness, tingling or pain). Currently, she says she feels tired almost all the time, and that the numbness in her legs has gotten worse and is sometimes painful.

Today she is in the clinic for a routine wellness appointment. At her last appointment her BMI was 29 and it is now 31, and she was re-starting a smoking cessation program with nicotine patches. Bloodwork from her last appointment showed her hemoglobin H1Ac was 6.2% (normal range <5.7%). Her family history is relevant for lung cancer (her mother died in her 50s) and cardiovascular disease (her father died in his 60s following a heart attack); both of her parents were "heavy smokers".

Question 3

What should be the primary care approach to prevention and management of cardiovascular disease in patients with MS?

A. Consult the package insert for the patient's DMT to identify specific guidelines for managing comorbid cardiovascular risks and disease

B. Neurologists will tailor the approach for each patient based on their symptoms and disability level

C. Follow the current recommendations in the American Academy of Neurology *Guidelines for the Management of Comorbid Conditions in Patients with MS*

D. Follow the current ACC/AHA recommendations

The approach to primary care for Allontae should essentially be the same as it would be for demographically similar patients. The studies that have been done suggest that comorbid conditions and lifestyle can affect MS symptoms, cognition, disease activity, and brain atrophy.[10,11] In this case, her increase in BMI should prompt diet, weight management and exercise counseling. Smoking is a risk factor for MS, and some studies have suggested that patients who smoke have worse disease at presentation, more signs of disease activity on MRI, faster disability progression, and earlier onset of secondary progressive MS.[12,13] Part of this wellness visit for Allontae should include a check in to see how her efforts to stop smoking are going, and if she needs any additional support or treatment to stop smoking since this is a major modifiable risk factor for disease worsening.

Cardiovascular, cerebrovascular, and metabolic disease are also prevalent and problematic comorbidities in patients with MS. A large, observational study suggested that patients with MS could be at risk of cardiovascular and cerebrovascular disease independent of other risk factors, and other studies have found faster disease progression, increased signs of MRI disease activity and poor outcomes (earlier loss of mobility, for example) in MS patients with comorbid hypertension, type 2 diabetes or dyslipidemia.[14,15] Allontae's H1Ac puts her at risk for type 2 diabetes and she should receive the same preventative treatment as other patients based on this.

The correct answer to the question is D. Patients with MS should receive the same preventative care and treatment for cardiovascular and metabolic disease from their primary care provider as other patients based on current guidelines (e.g., American College of Cardiology or American Heart Association). The DMT that she is receiving, and her MS symptoms should not affect the approach to health maintenance (although some symptoms, such as a loss of mobility, may necessitate modifications).

Some of Allontae's symptoms should be of interest since there can be overlap between them and untreated or worsening comorbid conditions. For example, Allontae has numbness and tingling in her extremities and fatigue. Changes in these symptoms are not necessarily due to MS, and a non-MS etiology should be ruled out. Fatigue, numbness or neuropathic pain, sensory symptoms (including visual disturbances), or bladder and bowel symptoms may not be due to worsening MS symptoms. Worsening paresthesia could be related to hypertension or metabolic disease, and these possible etiologies should be investigated. Fatigue is also common in patients with MS, but non-MS causes such as obstructive sleep apnea and sleep disorders should be excluded.[16-18] Depression, whether it is related to Allontae's fatigue or not, is underdiagnosed but common in patients with MS and should be screened for using standard clinical tools (e.g., the Beck Depression Inventory).[16,19,20]

Question 4

What should be the approach to cancer screening in patients treated for MS?

- **A.** Specific annual cancer screenings are recommended during and after discontinuation of monoclonal antibody treatments for MS
- **B.** Cancer screenings should start early for patients treated with most DMTs
- **C.** Cancer screenings for patients with MS should follow age- and risk-factor-based recommendations
- **D.** Cancer screening is the same for most MS patients except for those treated with one of a few DMTs used in patients with the most severe forms of MS

For most conditions, an MS diagnosis does not necessitate a change to preventative care screenings. In this case, Allontae should receive cancer screenings appropriate for her age and risk factors, and independent of her current DMT. While an increased rate of malignancy was noted during clinical trials for a few DMTs (e.g., cladribine, fingolimod and ocrelizumab), the actual increased risk is not known and there is no need for earlier or increased cancer screening in patients treated for MS.[21-23] Patients should be cautioned about the possibility of an increased risk for malignancy when discussing treatment options with their neurologist. The correct answer is C, primary care providers should follow recommendations based on the patient's age and risk factors.

Some adjustments to healthcare maintenance for MS patients are needed in just a few areas. Several DMTs are contraindicated in pregnant patients (teriflunomide and cladribine), and contraception is required or recommended for others. Teriflunomide is notable because both women and men treated with this DMT should be using contraception.[24] The choice of contraceptive in patients with MS is no different than for other patients: all of the current contraceptive options are considered safe and effective in patients with MS, and there are no known interactions between contraceptives and DMTs.[25,26] Disability or reduced mobility might be a consideration, and symptomatic treatments (such as carbamazepine) should be reviewed for possible interactions with contraceptives. During wellness visits, review patients' contraceptive use and reproductive plans, and ensure that they are communicating with their neurologist as their plans change.

Patients with MS should receive vaccinations according to the CDC's Adult Immunization Schedule, but the same precautions should be applied for patients on immunosuppressive DMTs as for other patients who are immunosuppressed.[27-29] Killed vaccines are considered safe, but live vaccines should be used with caution or, in some cases, not be used, depending on a risk-benefit assessment. Patients who are experiencing symptoms of a relapse should not be vaccinated until their symptoms have been stabilized or resolved, but patients can be assured that vaccination cannot precipitate a relapse. For patients who are starting or switching DMT, vaccinations may need to be scheduled around treatment.[29,30]

Routine laboratory work might be affected by some DMTs. Lymphopenia is the mechanism of action for some DMTs. When confronted with abnormal findings, check the patient's DMT to see if a known treatment effect can explain them. Liver function abnormalities can be an adverse event that should be raised with the patient's neurologist, as should recurrent or opportunistic infections. Patients who have been previously treated with alemtuzumab are at risk for autoimmune thrombocytopenia, renal disease, hepatic disease, and thyroid disorders and require long-term monitoring.[31]

Table 2. Disease Modifying Therapies with Labeled Warning or Precautions Against use of Live or Live-attenuated Vaccines*

Alemtuzumab[31]	Cladribine[21]
Fingolimod[22]	Ocrelizumab[23]
Ofatumumab[32]	Ozanimod[33]
Ponesimod[34]	Siponimod[35]
Teriflunomide[24]	
*Consult the prescribing information for specific guidance when considering live or live-attenuated vaccinations.	

Case Presentation 3: Identifying an MS Relapse in the Primary Care Setting

Robert is a 45-year-old Caucasian man who presents to the clinic because of urinary urgency and incontinence. He also notes new numbness in his feet bilaterally. His symptoms started about 2 weeks ago when he noticed abnormal urinary urgency during the day and nocturia. He has never had these symptoms before, and they seemed to just start happening one day. He does not think they have gotten worse, but he has had a couple episodes of urinary incontinence. His MS history includes diagnosis in his mid-30s after presenting with transverse myelitis. Initially he was treated with glatiramer acetate, and 10 years ago switched to teriflunomide so he did not have to inject daily. Since switching to teriflunomide he has not had any relapses and sees his neurologist once every 12 to 18 months. Other than some gait difficulty when he has to walk long distances, he does not think that MS affects his day-to-day life much. He is otherwise healthy, has no comorbid conditions and has no significant family history.

Question 5

Which of the following about MS relapses is true?

- **A.** Stress, an infection or non-adherence to treatment are the most common triggers for a relapse
- **B.** Symptoms are constant and last at least 24 hours
- **C.** Worsening of existing symptoms is more common than new symptoms
- **D.** Symptom severity may fluctuate considerably over the course of the relapse

The previous case considered how preexisting conditions could affect MS symptoms or mimic relapses. In this case, Robert's bladder symptoms could be due to an MS relapse, but other causes need to be excluded before contacting his neurologist.

Relapses vary from patient to patient and from one event to the next but there are some general characteristics they have in common. A relapse can involve new neurological symptoms or worsening of previous or existing ones, but the symptoms last at least 24 hours and have an acute or subacute onset (develop over hours or days). Thus, the correct answer is B. While the symptoms may gradually worsen over the course of the relapse, rapid worsening and resolution or fluctuation is not likely to be due to a relapse. Neurologic symptoms that do not meet these criteria are not an MS relapse and other possible causes should be investigated.

When patients experience transient worsening of symptoms or a reemergence of symptoms from a previous relapse, a non-MS cause should be considered. While stress or an infection cannot trigger a relapse, they (along with heat or fatigue) can lead to a transient worsening of existing symptoms; the symptoms should subside when the trigger is relieved or addressed.

Robert's symptoms meet the criteria for a possible relapse, both in their onset, constant severity and duration. Before concluding that he should see his neurologist, a primary care provider could investigate other possible causes for urgency and incontinence. If no other explanation for the urinary urgency and nocturia he is experiencing can be identified, he should see his neurologist to manage the symptoms of this relapse.

Asking about nonadherence to his DMT would be appropriate since nonadherence can increase the risk of relapse, but relapses are still possible even in patients who are adherent to treatment and have responded well. In this case, Robert has been using a once-daily oral DMT for a decade and has very little disease activity. Some studies have found that adherence to oral DMT is lower than for injectable or intravenous DMT, but other factors such as long periods of disease remission, the unpredictable disease course and comorbid depression can all contribute to nonadherence.[36-39] Encourage nonadherent patients to discuss how often and why they miss doses of their DMT so they can address the reasons for nonadherence or find a DMT that better meets the patient's needs.

Closing

This *eCase Challenge* focused on how to support MS patients by providing preventative healthcare and recognizing possible signs of MS between their visits to their neurologist.

The first case provided an overview of how to recognize a CIS, which is the first time a patient has neurological symptoms caused by the inflammatory processes that cause MS. Although not all patients who have a CIS will go on to have MS, they should be referred to a neurologist for evaluation and treatment of their symptoms.

The second case illustrated the important role primary care providers have in managing MS symptoms. Comorbid conditions can affect the risk of relapses, MS disease activity and long-term outcomes. In addition, some comorbid conditions can mimic or exacerbate MS symptoms. Ensuring patients' overall health is important to minimizing their MS symptoms and preventing disability worsening.

The last case showed how symptoms of a relapse can be evaluated in the primary care setting. Not all neurologic symptoms in an MS patient are caused by a relapse. Recognizing clinical presentations that are inconsistent with a relapse is an important step since they could identify the need for a primary care intervention. These cases demonstrate how primary care providers can contribute to managing MS by maintaining patients' overall health and recognizing when they need to consult their neurologist.

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Question #1
Neurologic symptoms caused by an MS relapse last at least:

- **A.** Several hours
- **B.** A day
- **C.** Several days
- **D.** A week
- **E.** A month

Question #2
Which of the following statements about diagnosing MS is correct?

- **A.** A spinal tap is often sufficient to confirm the diagnosis
- **B.** MRI is the fastest, most accurate method for diagnosis
- **C.** Inflammatory markers found in serum can confirm the diagnosis in patients with clinical symptoms
- **D.** No single test is likely to lead to a certain diagnosis

Question #3
Which of the following treatments often provided in primary care should be avoided in patients treated with an immunosuppressive MS disease modifying therapy?

- **A.** Specific anti-hypertensive treatments
- **B.** Epidurals
- **C.** Live vaccines
- **D.** Pharmacotherapy for smoking cessation

Question #4
As a primary care provider, what is your role in ensuring patients are adherent to their MS disease modifying therapy (DMT) between visits to their neurologist?

- **A.** Ask patients about adherence and barriers to taking their DMT
- **B.** Make dose adjustments to their DMT to help reduce side effects
- **C.** Prescribe symptomatic treatments for side effects
- **D.** Let the patient's neurologist assess adherence and address barriers

Question #5
As a primary care provider, what should your response be when patients present to you with new neurologic symptoms?

- **A.** Document neurologic symptoms and refer the patient to their neurologist
- **B.** Start a course of high-dose IV steroids and contact their neurologist
- **C.** Schedule an MRI and contact the patient's neurologist
- **D.** Exclude other causes that could worsen MS symptoms or cause neurologic symptoms

Question #6
What is the difference between a clinically isolated syndrome (CIS) and an MS relapse?

- **A.** A CIS is much shorter in duration
- **B.** A CIS only affects a single neurologic system while a relapse affects ≥2
- **C.** A CIS does not cause permanent disability
- **D.** A CIS is the first relapse that occurs in a patient not yet diagnosed with MS

Question #7
Which of the following is a presentation that is not commonly associated with a clinically isolated syndrome?

- **A.** Partial paralysis or weakness
- **B.** Complete transverse myelitis
- **C.** Painful eye movements
- **D.** Bilateral internuclear ophthalmoplegia

Question #8
In general, what considerations should you have when treating a comorbid condition (e.g., cardiovascular disease or diabetes) in a patient with multiple sclerosis?

- **A.** MS disease modifying therapies have many interactions with other drugs that need to be identified before starting a treatment for a comorbid condition
- **B.** The patient's neurologist is often better prepared to manage comorbid conditions in a way that will not impact their MS treatment
- **C.** An untreated comorbid condition can worsen MS symptoms and prognosis
- **D.** A patient's MS symptoms can limit what treatments and interventions can be used in patients with comorbid diseases

Question #9
Which of the following statements about cancer risk in patients treated with an MS disease modifying therapy (DMT) is accurate?

- **A.** Cancer risk is no different in patients with MS, regardless of which DMT they are treated with, than it is for patients without MS
- **B.** Cancer risk may be higher with some treatments, but does not require any additional or more intensive screening
- **C.** Some DMTs considerably increase the risk of cancer, and patients treated with these DMTs should start cancer screenings early
- **D.** Women treated with specific DMTs are at an increased risk of breast cancer during and for several years after treatment

Question #10
Which of the following is true about common primary care complaints and treatments in patients with MS?

- **A.** Using anesthesia or an epidural can increase the risk of a relapse
- **B.** Common vaccinations (i.e., for influenza or mRNA COVID vaccines) cannot be used during treatment with some DMTs
- **C.** An infection cannot trigger a relapse, but it can worsen MS symptoms
- **D.** Some antibiotics should not be used because they can increase the risk of a relapse

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