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Practical Insights on Multiple Sclerosis

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THE NEW Treatment Frontier Progressive MS

Up until now, the research focus in multiple sclerosis (MS) has largely been on relapsing forms of the disease—and the results have been life-changing with the release of 10 disease-modifying therapies (DMTs) since the 1990s. For many people, these DMTs can slow the progression of the disease and reduce the frequency and severity of their relapses. Now, however, researchers are focusing on a new frontier: progressive forms of MS. These are less common than relapsing MS but lead to more disability. (See "Ask the Clinician" on page 13 for a description of the four MS types.)

"We've always had an interest in progressive MS," says Timothy Coetzee, PhD, Chief Advocacy, Services, and Research Officer for the National MS Society, "but we haven't always had the tools to research it because there isn't an easy way to track progression the way we can with relapsing MS." In those cases, researchers can count the number of relapses people have or perform magnetic resonance imaging (MRI) scans to look for inflammation in the brain

and spinal cord. "We've had great success with developing therapies for relapsing MS, but that success hasn't been replicated in progressive MS, and that's just not acceptable," he says.

The trouble has been that "we don't understand what is happening in progressive MS," says Anne H. Cross, MD, professor of neurology and chair in neuroimmunology at Washington University in St. Louis, Missouri. "A lack of myelination leads axons to lose their protection and support. They become damaged and even die. We need to understand how to remeylinate axons and even regenerate the axons that have been lost."

The National MS Society, the National Institutes of Health, and other organizations are funding a wealth of research in this area. In addition, a coalition of MS societies from Canada, Denmark, Italy, the Netherlands, the UK, the US, and the MS International Federation have formed the Progressive MS Alliance, a global collaborative effort of committed MS researchers and experts. This unique alliance is making it a priority to accelerate clinical trials in progressive MS and understand the mechanisms behind the disease and

An MS Dictionary

Atrophy: Loss of brain volume as a result of tissue damage.

Axon: A fiber extending from the nerve cell body that conducts impulses to neurons or muscle fibers within the central and peripheral nervous systems.

Axonal loss: Destruction of the nerve fibers (axons), often leading to the death of neurons.

Central nervous system (CNS): The brain, optic (eye) nerve, and spinal cord.

Demyelination: Destruction of the protective myelin coating around axons.

Inflammation: A protective response of the body that can be good or bad. The immune system is believed to be overactive in MS, leading to chronic inflammation, which is damaging.

Myelin: The fatty insulating coating around axons that promotes the communication of messages between nerves and muscles, and protects and nourishes axons.

Neurodegeneration: Death of neurons.

Neurons: Impulse-conducting cells.

Remyelination: Creation of new myelin around axons.

how to treat it. They are also looking at how nerve cells are damaged in progressive MS and how to repair them, as well as attempting to develop better rehabilitation treatments and therapies for symptoms.

"Although it's taken a long time to make real headway, I am excited about the number of studies going on and I believe in a few years we'll see some new treatments become available for progressive MS," says Dr. Coetzee.

Some of the most promising avenues of research include:

- **Antibodies to the LINGO-1 molecule:** This molecule is found in the central nervous system and interferes with the body's repair of myelin and axons. An antibody has been discovered that is effective in blocking the molecule's actions and is being tested.
- **Idebenone:** This treatment is a man-made version of an antioxidant, one that is very similar to the common dietary supplement co-enzyme Q10. It may be able to protect the brain and spinal cord against damage that contributes to MS progression.
- **Ibudilast:** This oral drug has anti-inflammatory properties and protects nerves. It is being studied as a stand-alone agent and together with two other promising medications, amiloride and riluzole.

- **Laquinimod:** This oral drug reduced progression and lessened brain tissue damage in trials of people with relapsing MS, so a study of the medication in people with secondary-progressive disease is being planned.
- **Stem cell therapy:** Several different groups of investigators are looking at injecting patients with stem cells drawn from their own bone marrow to decrease immune activity and prompt tissue repair. Small preliminary trials have yielded encouraging results. Other researchers are testing whether skin cells can be reprogrammed and transplanted into the body to act as brain cells and to make new myelin.
- **NeuroVax:** This monthly vaccine doesn't prevent MS, but rather is a therapeutic vaccine that has been shown to calm a part of the immune system that attacks myelin in people with MS.
- **Ocrelizumab:** This intravenous drug is a monoclonal antibody that targets immune cells (B cells) and depletes them, which appears to calm the inflammatory process seen in MS.
- **Simvastatin (Zocor®):** In a recent study, this cholesterol-lowering drug was shown to reduce brain shrinkage, which is important for preserving cognition and function, compared to a placebo in people with secondary-progressive MS. A higher dose (80 mg) than

(Continued on page 8)

REHABILITATION FOR PROGRESSIVE MS

People with progressive MS have significant physical challenges. "Usually, because their disease is moderate to severe, they are not walking and they are wheelchair-dependent," reports Deborah Backus, PT, PhD, director of MS Research at the Virginia C. Crawford Research Institute at Shepherd Center in Atlanta, Georgia. "Combined with their lack of physical activity, they become deconditioned, which makes them weak and increases MS-related fatigue. These people have many barriers to exercising, and are stuck in a vicious cycle of functional decline."

Physical therapy and a good exercise program can help interrupt that cycle. It's even possible that some of the symptoms that appear to be a sign of MS progression might actually be more a result of deconditioning and a lack of physical activity. "With exercise, maybe we can help people with progressive MS become a little bit more mobile, more independent, and less fatigued," Dr. Backus says.

Dr. Backus and other rehabilitation specialists around the country and the world are looking at a variety of innovative exercise interventions. At Shepherd Center, for instance, her team is investigating the benefits of a functional electrical stimulation (FES) bike to see if it makes muscles stronger and healthier. Patients roll their wheelchairs up to the FES machine, position their legs on the pedals, place electrodes on their muscles that deliver electrical stimulation to make the legs move in a cyclical manner, and bike for about 30 minutes. Participants in the studies they've performed have reported that they enjoy using the bike, have positive feelings after their workout, have less pain, and think more clearly. It's also been noted that FES bike training has a positive impact on the respiratory system and metabolism. FES bikes are currently available in MS, rehabilitation, and outpatient centers, Dr. Backus says, and may someday be available at local gyms and YMCAs.

(Continued from page 6)

is prescribed for lowering cholesterol is used and there is a potential for muscle aches and a negative impact on the liver, so regular monitoring tests are required. Otherwise, the drug appears to be well-tolerated.

In addition, almost all of the DMTs that have proven effective in relapsing MS, including fingolimod (Gilenya®) and nataluzimab (Tysabri®), have been tested or are being testing for progressive disease.

Dr. Cross notes, "It's amazing what the field has accomplished in relapsing MS and I think we'll soon see the same progress in progressive MS. I expect things to move forward quickly."

Support Programs for MS Disease-modifying Therapies (DMTs)

Aubagio®, Genzyme Corporation:
www.aubagio.com, 855-MSONE2ONE (855-676-6326)

Avonex®, Biogen Idec:
http://www.avonex.com/multiple-sclerosis-support.xml, 800-456-2255

Betaseron®, Bayer HealthCare:
http://www.betaseron.com, 800-788-1467

Copaxone®, Teva Neuroscience:
http://copaxone.com/AboutSharedSolutions.aspx, 800-887-8100

Extavia®, Novartis:
http://www.extavia.com/info/PatientSupport/Patient-support-program.jsp, 888-NOW-NOVA (888-669-6682)

Gilenya®, Novartis:
http://www.gilenya.com/c/go-program, 800-GILENYA (800-445-3692)

Rebif®, EMD Serono/Pfizer Inc:
www.mslifelines.com, 877-447-3243

Tecfidera®, Biogen Idec:
http://www.tecfidera.com/support/ms-support-services.html, 800-456-2255

Tysabri®, Biogen Idec:
http://www.tysabri.com/ms-support-services.xml, 800-456-2255

MS News, Support, and Self-Help Groups

MS Views & News
www.msviewsandnews.org

MS World
www.msworld.org

Multiple Sclerosis Association of America
www.msassociation.org, 800-532-7667

Multiple Sclerosis International Federation
www.msif.org

Multiple Sclerosis Foundation
www.msfocus.org, 888-MSFOCUS

National Multiple Sclerosis Society
www.nationalmssociety.org, 800-344-4867

Bladder AND Bowel Issues IN MS

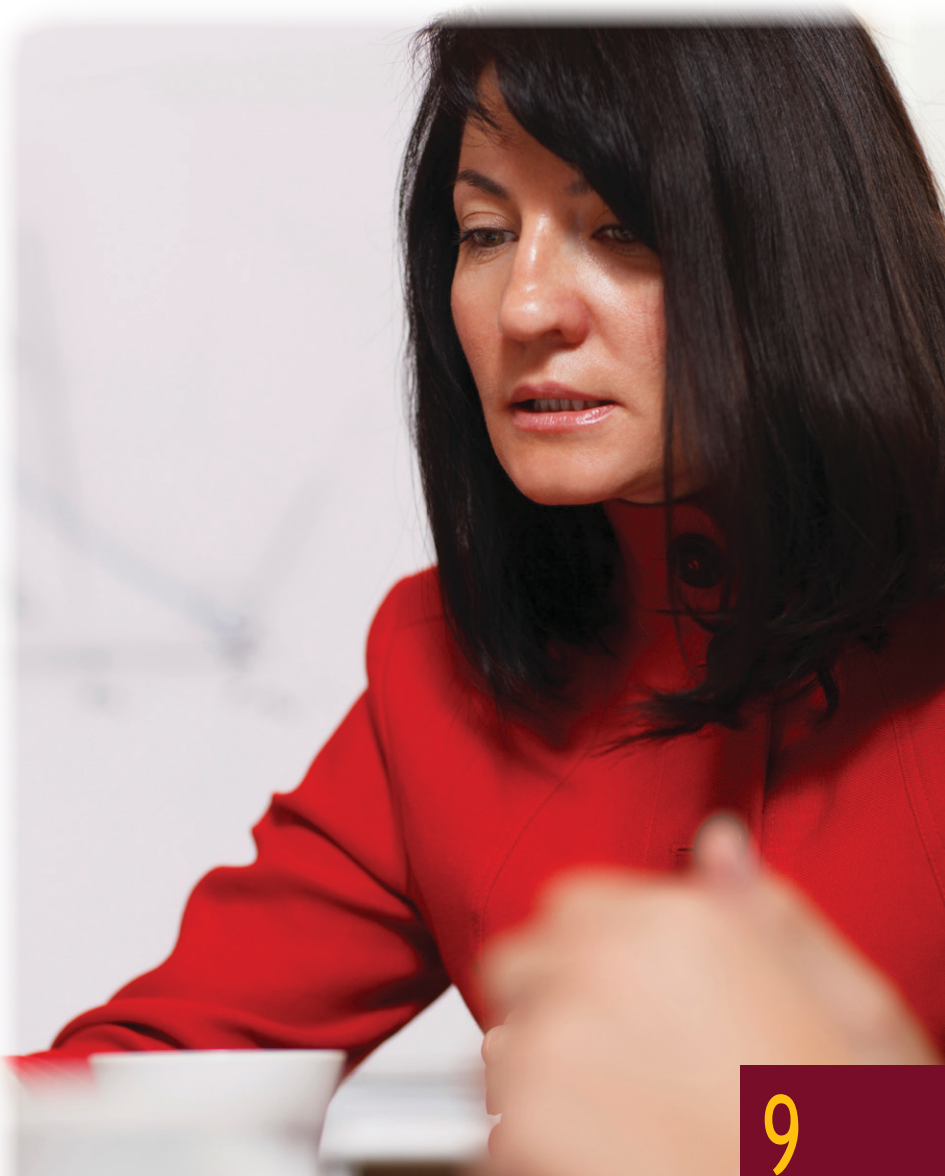
Bladder and bowel problems are common among people with multiple sclerosis (MS), particularly as the disease progresses. The discomfort can range from mild to severe, and can worsen during a relapse as well as contribute to relapses.

"Bladder and bowel symptoms in MS can seem overwhelming, but there are steps you can take to manage them," says Aliza Ben-Zacharia, DrNP, nurse practitioner at The Corrine Goldsmith Dickinson Center for Multiple Sclerosis of The Mount Sinai Medical Center in New York City and an *MS Perspectives'* advisor.

The Neurogenic Bladder

Due to nerve damage caused by MS, up to 75% of people with MS may develop a *neurogenic bladder*—meaning the nerve impulses that tell the bladder when to hold urine in the bladder and when to release it are disrupted, leading to a loss of control over their bladder function.

In general, there are two kinds of neurogenic bladder. If you have an overactive bladder, you are not able to



Common Symptoms of a Neurogenic Bladder

Overactive Bladder

- A frequent need to urinate
- A feeling of urgency—a need to urinate *now*
- Leaking or dribbling urine or loss of control
- Changes in the amount urinated
- Discomfort
- Waking up frequently during the night to urinate

Underactive Bladder

- Difficulty starting to urinate
- Not being able to empty your bladder
- Continued pressure in the bladder after you've urinated
- Leakage of urine from the bladder
- Urinary tract infections (UTIs)

control when or how much you urinate. When the nerve pathways in the spine are disrupted by MS, faulty signals can appear so that the presence of just a small amount of urine in the bladder will cause it to contract. This leads to a frequent need to urinate and a feeling that you have to empty your bladder *right now*—often when your bladder isn't even full. If the condition is severe, you might leak a little or even a lot of urine.

If you have an underactive bladder, you can't feel when the bladder is full, which leads it to store much more urine than it should. The bladder also doesn't completely empty when you urinate, and it may leak small amounts of urine as pressure builds.

"An underactive bladder is less common in MS than an overactive bladder," says Tracy Walker, FNP-C, nurse practitioner with the MS Institute at Shepherd Center in Atlanta, Georgia, and an *MS Perspectives*' advisor, "but it's more dangerous because it can lead to urinary tract infections (UTIs)." When urine is held too long, it can be a breeding ground for bacteria and infections of the bladder or ureters (the tubes that carry urine from each kidney to the bladder), and it can back up to the kidneys, causing irreversible damage. UTIs, in turn, like all infections, can trigger MS relapses.

Many people with MS may also suffer from detrusor sphincter dyssnergia (DSD), which makes it difficult to store urine—but also to release it. DSD bladders are also very prone to UTIs.

How Are Urinary Problems Treated?

Treatment of urinary problems is individualized. Typically, you will be told to stay away from bladder irritants such as caffeine, alcohol, and aspartame products in your diet, and to stop smoking if you smoke. (There is a higher incidence of bladder leakage in people who smoke, although it's not well understood how smoking triggers bladder issues.) You will be advised to drink a lot of fluids and to schedule regular bathroom breaks during the day rather than holding your urine until you are ready to burst. If these strategies don't help, your clinician may prescribe medication.

Bowel Problems

Healthy bowel function is a result of good communication between the brain, the spinal cord, and the intestine. In people with MS, these pathways are impaired. Like bladder dysfunction, the problem can be too little movement of the bowels, or constipation, which produces hard stools and infrequent bowel movements. Or the problem can be too much activity, or fecal incontinence, which is associated with bowel accidents, leakage of feces, or diarrhea (loose, runny stools). Impaired mobility and a lack of activity due to difficulty walking or fatigue can compound the problem by slowing the amount of time it takes waste to move through the intestine, and making it difficult for a person to get to the toilet

Common Constipation Symptoms

- Less than three bowel movements a week
- Hard stools
- Straining during bowel movements
- Stomach bloating or pain
- A sense of incomplete emptying
- Passing a lot of gas

before an accident occurs. Drugs used to treat MS and other conditions can also cause constipation, while laxatives used to manage constipation can cause bowel accidents.

As embarrassing as it may be to talk about these issues, it's better to suffer through an uncomfortable conversation than suffer with the symptoms of bowel disorders. And the good news is that there are ways your providers can help you with these issues.

Lifestyle changes are the best way to manage most bowel problems, starting with an increase in the amount of fiber you consume, which will make your stools softer and add bulk to them so they pass more easily. Good sources of fiber include whole grains, bran cereal, beans, fresh fruits and vegetables, prune juice, dried prunes, and over-the-counter fiber supplements. Be sure to drink plenty of fluids as you increase your fiber intake—the fiber will pull fluid from your colon and add it to your stools, again bulking them up and making them softer to pass.

It's also important to get regular physical activity to improve your digestion and elimination. If you can't perform regular exercise programs, ask a physical therapist to create a program for you that you can do.

Next, start to eat and plan to eliminate on a regular schedule. Choose a convenient time about 20 to 30 minutes after you've had a warm meal or beverage to have a bowel movement.

Finally, if these changes don't do the trick, ask your provider about taking a laxative to make your stools easier to pass. For people suffering from diarrhea or fecal incontinence, over-the-counter antidiarrheal agents and bulking agents can be used.

Ask the Clinician

Our 4 Medical Advisors Respond

Q. How do I know what kind of MS I have—relapsing-remitting, progressive-relapsing, secondary-progressive, or primary-progressive?

Barbara Green, MD

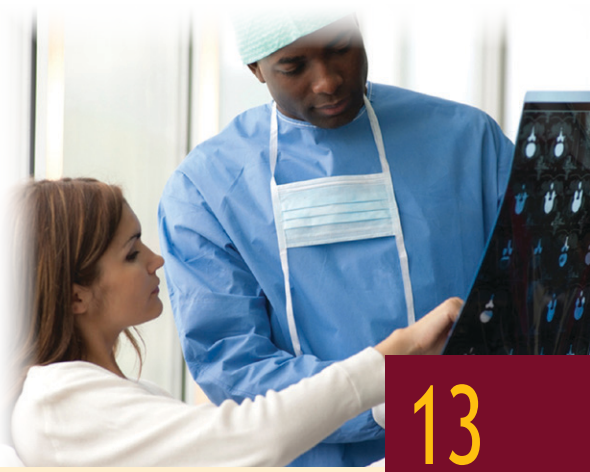
A. Categorizing the clinical types of multiple sclerosis has become increasingly important as the number of treatment options for managing the disease expands.

In **relapsing-remitting MS (RRMS),** the disease presents as attacks of new or recurrent symptoms (think visual loss, numbness/weakness in the arms or legs, dizziness, or gait changes). An attack lasts days to weeks and may or may not result in continuing disability.

Secondary-progressive MS (SPMS) is a category only assigned to patients who began with RRMS and transition into a slow worsening of disability with rare or no actual attacks, and with magnetic resonance imaging (MRI) scans that often show no new disease.

Primary-progressive MS (PPMS), typically seen in the MS patient who is first diagnosed over the age of 40, has a slow onset of neurologic loss that then continuously progresses. Although these patients may experience plateaus of stability without new deficits, they never have any attack followed by recovery that characterizes the relapsing forms of disease.

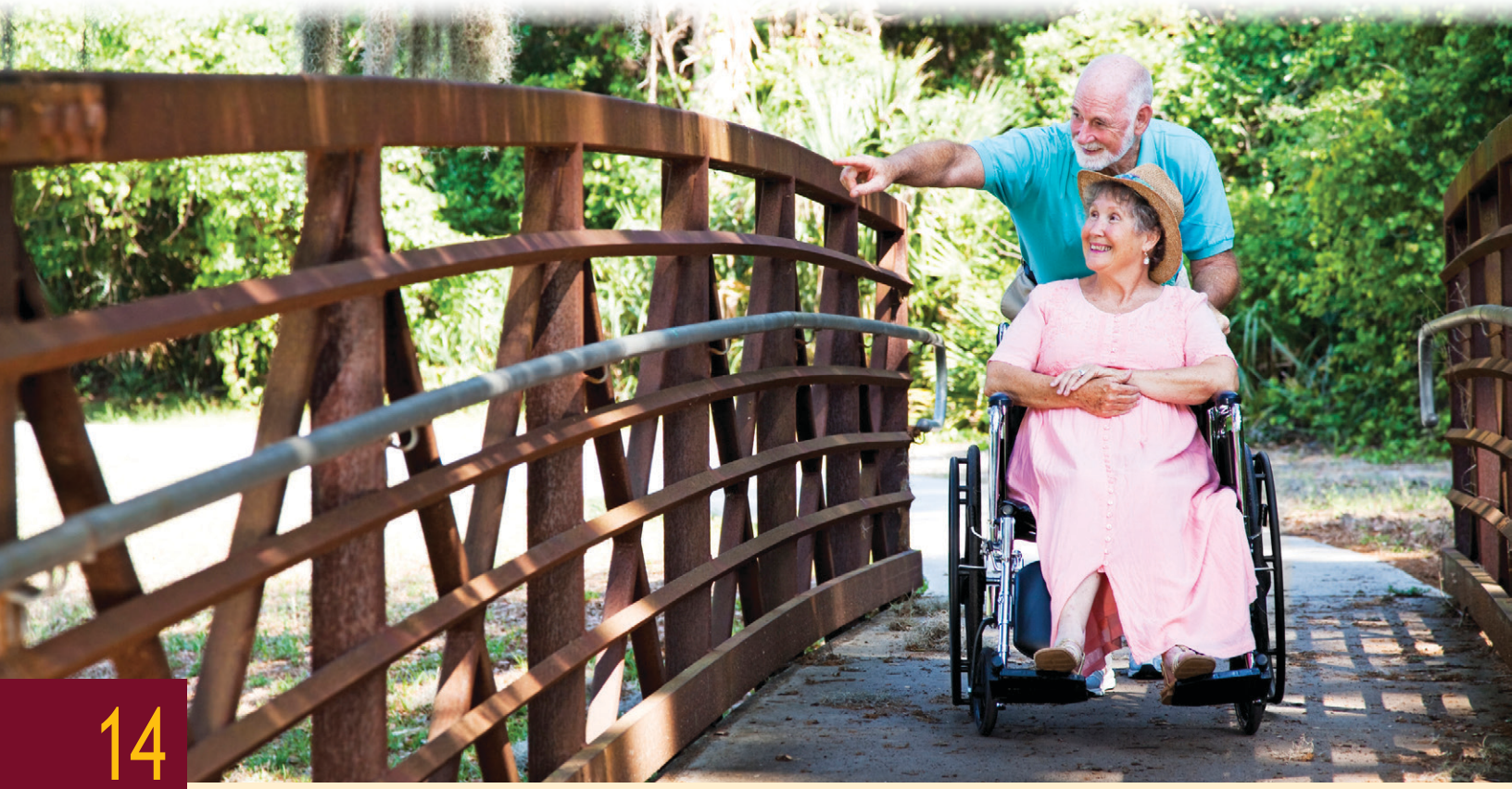
The fourth and final clinical category for MS is termed **progressive-relapsing MS (PRMS)**. Seen in fewer than 5% of patients, this disease pattern looks identical to PPMS most of the time. Occasionally, however, a bona fide relapse will occur during the mainly progressive course of the disease.



Barbara Bishop,
MS, ANP-C, MSCN, CNRN

A. Why is it important to know what category you fall into? Whether we are talking about MS or any other disease process, categories were historically developed to assist researchers in figuring out who to include in clinical trials and who not to include, which in turn helps us avoid results that may be misleading, difficult to interpret, or inconclusive.

Another reason disease type is important is because it helps us to determine treatment options. For example, almost every disease-modifying therapy (DMT) is approved for relapsing forms of MS. The drugs' effects have been demonstrated through research and the medications have been approved by the Food and Drug Administration (FDA) for these types. Sometimes, however, disease "type" can get in the way of treatment and intervention. To date, we have yet to have a drug approved exclusively for progressive forms of MS. That's not to say that the existing drugs for relapsing MS may not be effective for people with progressive disease. It is to say that the study of these drugs hasn't shown much impact on the progressive MS disease course—perhaps because we don't know the signs to look for. That's why we're now working to identify ways to better evaluate the effectiveness of DMTs in progressive MS.



Aliza Ben-Zacharia, DrNP

A. It is mainly important to identify the type of MS a person has for clinical trials, so we can determine the best DMTs for different types of the disease. It is not always helpful, however, to fit patients into boxes and types—sometimes, it is important to think outside of the box. Often, we treat all patient types with a DMT when there is evidence of activity clinically (new symptoms or signs of the disease) or radiologically (on your MRI scan).

You do not want to be on a medication that does not treat your MS, but regardless of type we don't have any reliable ways to help us figure out which DMT will be the best for any one individual. Therapy is really based on trial and error. The research data is mostly focused on the benefits of DMTs for controlling relapsing-remitting MS. Although we do not have data for progressive forms of MS *yet*, we still use these DMTs when we see that the disease is active.

Tracy Walker, FNP-C

A. The four categories used to describe MS were developed based on the natural history of the disease—before we had treatments that could alter the course of MS. Now we have DMTs that can slow the progression of MS and prevent or reduce the frequency and severity of relapses. Sometimes it can be difficult to tell which category best describes your disease if you have been on a DMT. We have some tools that we use to help us, such as MRI, the Expanded Disability Status scale (EDSS), and your medical history. If someone has a clear-cut relapse or active MRI lesions, then we may be confident they truly have relapsing-remitting MS. The harder call is when people have not had any clear-cut relapses and no changes on MRI, but they feel they are slowly worsening. The question then becomes is the medicine preventing relapses and slowing progression but not completely stopping it? Or is this patient's MS more of a progressive type?

It is human nature to want things to fit neatly in categories and behave the way they should. Unfortunately, reality is usually not that ordered and predictable. So don't get discouraged if you ask your medical provider what type of MS you have and the answer starts with "Well, I think it's…."

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