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Practical Insights on Multiple Sclerosis

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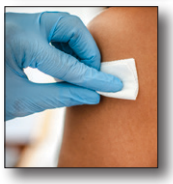

Disclaimer: The goal of this publication is to provide patients with multiple sclerosis with the latest information about the disease and its treatment. The information provided in *MS Perspectives™* is not a substitute for the advice of your healthcare nurse or doctor. Please consult a qualified healthcare provider for individualized care and information.

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EMERGING LONG-TERM DATA

About Disease-Modifying Therapies (DMTs)

There are many treatment options now available for relapsing forms of multiple sclerosis (MS), and you may be curious about how the safety and effectiveness of these drugs are determined so they can be released onto the market.

Clinical Trials Before and After Drug Approval

Before approving a medication for use, the Food and Drug Administration (FDA) requires drug manufacturers to complete a series of clinical trials that show it is both safe and effective for a particular disease. Information about the results of these trials can be found in the drug's product insert (PI) and patient guide, and is worth reading and discussing with your clinician as you decide which disease-modifying therapy (DMT) is right for you at this time of your life and based on your individual MS profile.

The story of a medication does not end at the time of its release onto the market, however. Instead, as more and more individuals are prescribed a DMT outside of the setting of a controlled clinical trial, more and more information is compiled for that drug. This "real-world" information allows researchers and clinicians to continue to assess both its effectiveness and safety. In addition, all prescribers of a medication contribute to a drug's database by reporting serious side effects or toxicities that arise when they put patients on the drug in question. Those reports are then accumulated, both by the pharmaceutical company manufacturing the medication and by the FDA, and may result in an update to the PI's list of side effects. In cases of dangerous reactions, toxicities, or drug interactions, the FDA may require that the PI carry a boxed warning.

Extension Studies and Post-Hoc Analyses

Patients participating in the original pivotal trials of a medication may be followed for a number of years after the initial trial ends. Like the real-world data mentioned above, these so-called extension studies continue to measure clinical outcomes and assess safety over the long-term. Study investigators may also re-examine the accumulated data from a trial to ask a different question about a drug: For instance, if they didn't look at mobility in a study of a DMT but they have data from the trial participants relating to ambulation, they might look at that. Such investigations are referred to as post-hoc analyses and are useful in gaining additional insights into the medication or to the disease itself.

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New Information from MS Meetings

Besides the PI, additional information about MS medications already on the market reaches clinicians through journal articles and presentations at research meetings. New data on several of the DMTs for MS were recently presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) meeting held in Fall 2018. Following are some highlights of interest about long-term use of certain DMTs for patients with relapsing MS.

Teriflunomide (Aubagio®)

Analysis of long-term data pooled from three large, placebo-controlled trials provided information on patients using Aubagio® for up to 12.8 years. In this extension study, the relapse rate on an annual basis remained lower (decreased by 35%) than the relapse rate among subjects in the placebo groups, and patients' disability scores remained stable. No new safety concerns were raised over the many years of the extension trial.

Another presentation of interest at ECTRIMS was a report on changes in whole brain volume (brain tissue) related to use of Aubagio®. Brain volume measurements are increasingly thought to represent an important outcome in MS treatment, with loss of brain volume being associated with more progressive and disabling disease. Researchers performed a post-hoc analysis of patients with clinically isolated syndrome (a first instance of a neurologic attack that may progress to MS). Magnetic resonance imaging (MRI) scans performed over 24 months showed that in the group of patients on 14 mg of Aubagio®, the brain volume loss was 43% less than in people on a placebo.

Fingolimod (Gilenya®)

A real-life, open-label study of 4,229 patients in Germany on Gilenya® treatment for 5 years found that the annual relapse rate remained stable through the 5-year follow-up period. (An open-label study is one in which participants know what drug they are receiving.) The Expanded Disability Status Scale (EDSS) score was an average of 3.0 at baseline (the start of the study) and 3.1 at 5 years for those who completed the entire study (726 patients). The safety profile in this study group was comparable to that seen in the original controlled pivotal trials for Gilenya®. The most common side effects included upper respiratory infections, liver enzyme elevations, and one case of progressive multifocal leukoencephalopathy (PML), a serious complication of Gilenya® that has been added to the PI since the original approval of the drug. In a subset of patients given a cognitive test called the Symbol Digit Modalities Test (SDMT), cognition (thinking, memory) was stable at 5 years. Thus, overall, this trial appears to confirm the known benefit/risk profile of this medication.

Additional confirming data were presented in LONGTERMS, an extension trial of the original Gilenya® pivotal trials. The reduction in the relapse rate at 5 years was 0.89 compared to 1.35 at year 1 in the trial. In addition, 78% of the participants did not experience progression of disability during the 5 years.

Alemtuzumab (Lemtrada®)

Eight years of follow-up data on the original participants of the CARE MS I and CARE MS II trials were also presented at ECTRIMS. In an open-label extension trial, 56% of Lemtrada®-treated patients required no additional courses of the drug or any other DMT through year 8 from the start of the study. The annual relapse rate at year 8 was less than one relapse a year. Eighty-eight percent of the patients were relapse-free and 78% were stable to improved as measured by their EDSS score. Adverse events were decreased in years 3 to 8 as compared to years 1 and 2 of the study.

One additional analysis evaluated patients who required a 3rd course of medication due to breakthrough disease after they received the standard two infusion courses in years 1 and 2. These patients (325 out of the original total of 811 Lemtrada®-treated study patients) received the 3rd course on average 2.5 years after the 2nd course was administered. This resulted in improved outcomes over the next 3 years of follow-up. The safety outcomes for this group were no different than for the patients who only received the standard two courses.

New data from patients in the two pivotal trials who developed thyroid abnormalities as a complication of Lemtrada® were also presented, and showed that the occurrence of this problem did not have a negative effect on patients' quality of life.

HOW DO Disease-Modifying Therapies (DMTs) WORK?

A frequent question that many patients ask me is: "If my current disease-modifying therapy (DMT) is not working, will changing to a different one make a difference?"

The dynamics of how DMTs stabilize multiple sclerosis (MS) are complicated and based on how the drugs interact with the immune system, and there is currently no way for your healthcare provider to predict exactly how a particular DMT will work for you: There are no blood tests or other biological or genetic markers that forecast better outcomes with one drug over another for an individual patient. But we do know that each of the classes of drugs fights your MS in different ways—what's known as its mechanism of action (MOA).

Often, your provider will have a discussion with you about how a DMT is given, what the side effects might be for you, and the risks of a specific DMT versus its benefits, but the drug's MOA might not be discussed. Ultimately, though, the MOA can be an important factor in your body's response to the DMT. Given that fact, here is a breakdown of the different classes of drugs currently on the US market and how they work.

Interferons (Avonex®, Betaseron®, Extavia®, Plegridy®, and Rebif®) lessen how much the MS disease process disrupts the blood-brain barrier, thereby reducing the amount of inflammatory immune cells (T and B cells) that get into the central nervous system. Interferons are also thought to affect T and B cells and immune-system proteins called cytokines by increasing the production of anti-inflammatory cells/cytokines and suppressing production of inflammatory cells/cytokines that promote inflammation in MS. Ultimately, this leads to a reduction in MS activity.

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Glatiramer acetate (Copaxone®, generics) is thought to create a shift from production of pro-inflammatory T cells and cytokines to anti-inflammatory T cells and cytokines. There is also evidence that this drug may have a broader effect on both the immune system you were born with, and the one that has developed over time in response to your environment. This leads to reduced MS activity.

Fingolimod (Gilenya®) belongs to a class of drugs called sphingosine 1-phosphate (S-1-P) receptor modulators. By affecting the S-1-P receptor, white blood cells called lymphocytes remain trapped in lymph tissue, which reduces the amount of inflammatory cells circulating in the bloodstream that are available to cause MS activity.

Teriflunomide (Aubagio®) inhibits an enzyme called dihydroorotate dehydrogenase (DHODH) that is needed for active T and B cells to function. It stops these cells from proliferating (rapidly increasing in number) but does not kill them.

Dimethyl fumarate (Tecfidera®) has an anti-inflammatory effect on the body by stimulating the so-called Nrf-2 pathway. This effect is also believed to help prevent damage to cells caused by MS.

Mitoxantrone (Novantrone®) is currently the only drug approved by the Food and Drug Administration to treat secondary-progressive MS and rapidly worsening relapsing-remitting MS, but it is generally not used due to serious long-term side effects such as heart failure and leukemia. It is a cytotoxic agent, which means it kills cells. It also inhibits proliferation of T and B cells.

Natalizumab (Tysabri®) is a monoclonal antibody [MAB]. It is believed to directly inhibit the movement of white blood cells across the blood-brain barrier into the central nervous system, thus reducing the formation of MS lesions. It does this by binding to what are known as adhesion molecules.

Alemtuzumab (Lemtrada®) is also a MAB. It targets B and T cells that have a surface protein on them called CD52. It depletes CD52 B and T cells, and is believed to encourage lymphocytes (white blood cells) to react in a more normal way.

Ocrelizumab (Ocrevus®) is another MAB, and reacts against a surface protein called CD20 that is found on B cells, reducing their numbers. (It does not target T cells.)

Different MOAs Mean More Options

MS is a very individual disease for each patient, and people can react differently to different DMTs due to their MOA. They can even respond initially to an MOA and then stop responding to it or not respond as well as before. Having DMTs that attack the immune system from many different angles is to our advantage.

Bottom line: If you are not doing well on your current DMT—you are having relapses, your scans show more disease activity, your disability is getting worse, or you are experiencing significant side effects—you might want to talk to your MS clinician about a drug with a different MOA. It may make a difference for you.

Support Programs for MS Disease-Modifying Therapies (DMTs)

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

Avonex,® Biogen:
www.avonex.com/en_us/home/above-ms-program/join-biogen-support.html, 800-456-2255

Betaseron,® Bayer HealthCare:
https://www.betaseron.com/why-betaseron, 844-788-1470

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

Extavia,® Novartis:
www.extavia.com/info/PatientSupport/patient-support-program.jsp, 866-EXTAVIA (866-398-2842)

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

Glatiramer Acetate Injection, Mylan
https://www.glatirameracetate.com/en/patient-support 844-695-2667

Glatopa,® Sandoz:
www.glatopa.com/glatopa_care, 855-GLATOPA (855-452-8672)

Lemtrada,® Genzyme:
www.lemtrada.com, 855-MSONE2ONE (855-676-6326)

Ocrevus,® Genentech:
www.ocrevus.com, 844-OCREVUS (844-627-3887)

Plegridy,® Biogen:
www.plegridy.com, 800-456-2255

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

Tecfidera,® Biogen:
www.tecfidera.com, 800-456-2255

Tysabri,® Biogen:
www.tysabri.com/en_us/home/join-biogen-support/join-biogen-support.html, 800-456-2255

MS News, Support, and Self-Help Groups

Can Do Multiple Sclerosis
www.mscando.org

MS Views & News
http://www.msviews.org/msviewsandnews4

MS World
www.msworld.org

Multiple Sclerosis Association of America
http://mymsaa.org, 800-532-7667

Multiple Sclerosis International Federation
www.msif.org

Multiple Sclerosis Foundation
www.msfocus.org, 888-MSFOCUS (888-673-6287)

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

UPDATE

ASSISTIVE DEVICES
FOR PEOPLE WITH MS

Symptoms of multiple sclerosis (MS), such as muscle weakness, loss of balance, tiredness, pain, impaired sensation, and difficulty walking, can increase a person's risk for falls. In these cases, several options exist to help improve your walking ability and reduce your falling risk. These include:

1) a variety of braces (orthoses);
2) stability aids such as canes, forearm crutches, and walkers;
3) devices known as neuro-prosthetics that provide functional electrical stimulation (FES) to your muscles to prevent foot drop (a condition where it is difficult to lift the foot when you walk due to nerve damage from MS);
4) power mobility aids (primarily scooters and wheelchairs) that are used when you are not able to walk distances or when you can't walk at all; and
5) robotic exoskeletons that are used to either train you to improve your walking or allow you to walk for exercise during rehabilitation sessions.

Exoskeletons

Starting first with the most revolutionary mobility aids for people with the greatest amount of disability, exoskeletons are robotic devices that are worn outside a person's clothes and around the trunk, hips, legs, and feet. They are designed to act as artificial musculoskeletal systems. The levels of powered robotic assistance can be adjusted to meet each person's unique needs.

Exoskeletons used in neuro-rehabilitation were originally developed for people with spinal cord injury and paralysis due to stroke. However, the use of exoskeletons in rehabilitation for persons with MS has been growing. "We've been using lower-extremity exoskeletons for the past couple of years in our rehabilitation programs for people who have difficulty walking or who are unable to walk at all," says Clare Hartigan, PT, MPT, a physical therapist at the Andrew C. Carlos Multiple Sclerosis Center at Shepherd Center in Atlanta. "The external support and power from the exoskeleton device allow patients to stand up and walk." Using an exoskeleton as a therapeutic tool has the potential to improve strength, balance, motor control, posture, cardiovascular health, and mobility. "While using an exoskeleton won't change the course of MS, there are many health benefits to standing, walking, and exercising," she says. "Being upright, in combination with exercise/mobility, has been shown to improve bowel and bladder function, as well as reduce spasticity (muscle stiffness) in people with spinal cord injury. If such devices have been shown to help individuals with spinal cord injury, it makes sense that they also have the potential to help those with MS."

Photo Credit: ©Parker Hannifin Corporation

Two exoskeletons are available in the United States for use at over 100 rehab facilities nationwide (and you can find a center by visiting the websites below):

- EKSO (photo on the cover), a 58-lb. device, was the first exoskeleton to be approved by the Food and Drug Administration (FDA) in 2015. Learn more about it at https://eksobionics.com/eksohealth/.
- Indego (photo, left) is a 30-lb. device that was FDA-approved in 2016. Learn more about it at www.indego.com.

Neither of the devices listed above are approved by the FDA for use by people with MS. However, clinicians at several rehab facilities who have one or both at their

center feel comfortable using them off-label, says Ms. Hartigan. Both devices can be custom-fit to an individual's body through adjustments of the external hardware.

To use an exoskeleton, patients must have good range of motion and strong bones. There are also height and weight restrictions—in general, you have to be 6'3" or less and weigh 220 lbs. or less.

A third robotic device that is available in Canada, called the Keeogo (https://keeogo.com), is being studied in the US and is designed for daily use to help people walk farther and longer, go up and down stairs, and stand and sit easier. It is designed to reduce stress on the knees in particular.

Photo Credit: ©Walk-Aide

Functional Electrical Stimulators

For people with foot drop, FES devices are used to stimulate the nerves in the leg muscles to lift the foot. As a result, persons with MS may be able to walk with a smoother gait, have a decreased risk for tripping and falling, and may be able to walk longer distances without feeling tired. Two such devices commonly used in rehabilitation across the US (Bioness, www.bioness.com and Walk-Aide, www.walkaide.com) are lightweight and battery-operated, and are meant to be used every day in the home and community, says Ms. Hartigan. To use FES devices, you need to have good range of motion at the ankle and the ability for the anterior tibialis muscle (the long muscle on the front of the lower leg) to contract in response to the stimulation. Not all people with MS respond to FES.

One limiting factor with FES devices for foot drop is their cost. According to Ms. Hartigan, depending on the device options required by the person, they can cost anywhere from $7,000 to $15,000. Unfortunately, not all insurance companies cover the cost and they are not covered at all by Medicare or Medicaid. FES devices are not recommended for persons who, in addition to foot drop, also have severe hyperextension of the knee (meaning the knee joint goes backward when the foot is on the ground).

Advancements in Braces

There have been many technological advancements in prefabricated carbon fiber and custom-molded polypropylene braces, too, says Ms. Hartigan—in particular, the plastics and joints used for custom-molded braces have gotten lighter and carbon fiber braces have become more durable. Additionally, the amount of control a brace can provide has been improved thanks to creative modifications.

"If you received a brace 5 or more years ago, it is probably bulkier and heavier than it needs to be, so you should see a PT for an evaluation," she says. The cost of prefabricated and custom braces is typically covered by private health insurance as well as Medicaid and Medicare, making them accessible to nearly all people with MS who need them.

You should also see a PT to ensure that you are using the appropriate stability aid. "Whether you use a cane, a forearm crutch(es), a walker, or a rollator (a walker on wheels), it can have a huge impact on your walking, balance, and level of fatigue," says Ms. Hartigan. "I have seen hundreds of patients over the years with MS who improved their walking simply by using a lightweight brace or FES device and/or changing their stability aid." She recently had a patient who had a history of falls, foot drop, and significant fatigue when walking with her cane. But when she started using a lightweight ankle brace and changed to a single forearm crutch instead, she stopped falling and could walk longer distances with less fatigue.

Service Dogs for People with MS

Jill Leverton, a retired physician with secondary-progressive multiple sclerosis (SPMS) who uses a wheelchair, has never considered herself a "dog person." Yet as her MS progressed, she decided to apply for a service dog. "I didn't want to have to rely on other people for everyday things, especially when my husband was sometimes away from home," she says. At that point in time, she was using a cane, and Jewel, her first assistance dog, came to her fully trained at 2 years of age and excelled at retrieving her dropped cane.

"It took Jewel a while to adjust to my routine, but once we were comfortable together, she gave me the confidence to go out in the world by myself," Dr. Leverton says. After Jewel was retired at 10 years of age, Dr. Leverton received Willemina, whom she calls Mina. Currently 6 years old, "Mina is great at picking things up for me, from my car keys to pencils, paper clips, and ointment tube caps. She is a wonderful dog."

Dr. Leverton obtained her assistance dogs free of charge from a national organization called Canine Companions for Independence®, the oldest (founded in 1975) and largest group in the United States to provide service dogs. (The group placed 400 dogs with individuals in 2017.)

"Canine Companions was the first group to offer assistance dogs for people with disabilities other than blindness," reports the group's public relations and marketing coordinator, Michelle Williams. These dogs act as the hands, legs, and ears of their human partners as needed, as well as loving companions. As Dr. Leverton experienced, they are trained to perform some 40 tasks that can be difficult for people with MS to accomplish, such as helping them get in and out of chairs and beds using a "tug" command, picking up and delivering

All photos courtesy of Canine Companions for Independence®

Dr. Jill Leverton and her service dog Mina.

dropped items, turning lights on and off, and opening and closing doors. "The goal is to have the dogs perform practical tasks for people so they don't have to rely on their family and friends as much, enhancing their independence," says Ms. Williams.

The non-profit breeds its own dogs—Labradors, golden retrievers, and crosses of the two breeds—and relies on volunteers to raise them to approximately 18 months of age. At that point, the dogs go into professional training for 6 to 9 months before being matched with a person with MS or another disability. "People who have applied to and been accepted into the Canine Companions program spend 2 weeks on our campus going to lectures, performing commands, and getting to know different dogs," explains Ms. Williams. "During this time, our trainers observe the clients and dogs together to make a perfect match." Once the human-canine pairs return home, the organization continues to provide assistance to ensure the relationships are beneficial.

Due to high demand and the cost of training assistance dogs (about $50,000 over the lifetime of the animal), it takes approximately 2 years from first application to being matched with a dog. Applicants must demonstrate a need for an assistance dog as well as the financial and physical means to care for the dog.

On the other end of the spectrum, the working lifespan of a dog is typically around 8 to 10 years. "As the dogs get older, around 12 years, they are retired as service animals and kept as pets by our clients or adopted by others," says Ms. Williams, adding that clients can then apply for a successor dog.

"Having a service dog is different than having a pet dog," Dr. Leverton notes. "You still have to groom, feed, and walk the dog like a pet, but you also have to work with her so she remembers her commands and can perform the tasks you need her to. And, of course, you can take a service dog along with you to many places that you can't bring a pet dog, which really opens up your world."

Service Dog Resources

Assistance Dogs International
Visit this group's website for programs in your area that train and place service dogs.
assistancedogsinternational.org

Canine Companions for Independence®
Canine Companions is the oldest and largest non-profit service dog group in the United States providing canine assistance for people with MS and other disabilities.
www.cci.org

International Association of Assistance Dog Partners
IAADP's website allows you to ask questions and obtain information about service dogs from people within the assistance dog community.
www.iaadp.org/

Paws with a Cause®
Paws with a Cause® breeds and trains assistance dogs for people with physical disabilities, severe chronic illness, or a neurological disorder such as MS, hearing loss, seizures, and autism.
www.pawswithacause.org

MS and Other Illnesses: What Are the Connections?

Many people with multiple sclerosis (MS) also have other illnesses (known as comorbidities) such as high blood pressure, diabetes, high cholesterol levels, migraine headaches, depression, and anxiety. Because comorbidities are so common, the medical community has recently begun to focus on the association between them and MS. Canada, having a universal healthcare system, is an ideal place for looking at these associations, according to Helen Tremlett, PhD, Canada Research Chair in Neuroepidemiology and MS, and Professor in the Faculty of Medicine (Neurology) at the University of British Columbia in Vancouver.

Helen Tremlett, PhD

"In British Columbia, for example, all individuals have a unique identifying number and every time a person accesses the health system, information is captured—every prescription filled, every hospitalization, every physician visit, and all births, deaths, and information such as socio-economic status, age, and sex," she explains. It takes time and considerable effort to access the data, and it first must be linked and then made anonymous to fulfill privacy and ethical requirements. When it is eventually released to researchers, however, it offers a treasure trove of information to be mined and utilized to answer important health questions. (While the United States compiles similar data, it can be more difficult for researchers to utilize it, in part because healthcare information can be spread across many different public and private healthcare plans.)

Four Key Questions

In MS, Dr. Tremlett and her colleagues have used the Canadian data, including that from British Columbia, to look at four key questions.

1. Is MS associated with an increased risk of cancer? Actually, no, she says: The overall cancer risk was lower than expected among people in British Columbia with MS, as compared to the matched general population. Although researchers do not fully understand why there is a reduced risk, it may be because the immune system is "hypervigilant" in people with MS and helps to remove emerging cancer cells. Or perhaps people with MS have a genetic predisposition that increases the risk of MS but reduces cancer risk. It is also possible that people with MS may lead healthier lifestyles to combat their chronic illness, which may help reduce the risk of cancer. It is worth noting that these are all hypotheses and have not been proven, Dr. Tremlett says. Also, people with MS should be aware that they can still get cancer and should participate in cancer screening programs offered in their area. "It's also not known what impact newer disease-modifying therapies (DMTs) will have on the risk of cancer," she says, so while the overall message appears positive, there is still much to be understood.

2. Does having a comorbidity alter the chance that a person with MS will start a DMT? It may, Dr. Tremlett says. "People with MS and comorbidities were less likely to start on a DMT than people without comorbidities, according to our data, and it appears that treatment decisions regarding DMTs in MS are being affected by the presence of specific comorbidities." She adds that people with comorbidities have often been excluded from MS clinical trials of DMTs, so more research is needed in this area.

3. Are comorbidities associated with relapses or progression of disability? Yes, potentially, according to Dr. Tremlett. Three studies suggest that having more comorbidities (three or more) leads to a higher relapse rate and progression of disability than not having any comorbidity. Also, having high cholesterol levels or migraines along with MS has been associated with an increased relapse rate, while mental health issues, heart disease, and epilepsy appear to increase disability as measured on the Expanded Disability Status Scale (EDSS).

(Continued on page 15)

Your Journey to...

WELLNESS

MS & Vaccines

Multiple sclerosis (MS) experts and patients are often concerned about the safety of routine vaccinations as well as those required for travel to other countries. In addition, certain disease-modifying therapies (DMTs) for MS may interfere with the development of the desired immune response associated with the vaccine (notably, the development of antibodies to a virus or bacteria).

You should have a discussion with your healthcare provider every year about what vaccines you might need. Often the discussion will revolve around the ratio of risks to benefits for you in regard to the type of MS medications you are taking. It is also always important to have a blood workup to determine your immunity to several viruses (such as the shingles virus) before starting a new DMT, and then be vaccinated as needed if the vaccines are safe for you.

There is evidence that supports different strategies, including the use of vaccines, to minimize the risk for infections, since it is known that infections may trigger an MS relapse. Certain vaccines are considered fairly safe for people with MS to receive, such as inactive, non-live vaccines like the seasonal flu shot (but not the nasal spray that contains live virus) and pneumonia vaccines. (See the table on page 13.) However, live and live-attenuated (live but weakened) vaccines such as that for yellow fever are usually not recommended for patients with MS, since they may trigger an MS change, such as an attack or progression of disability.

Guidelines on Vaccines

A systematic review of 130 studies was published in 2002 and authored by physicians and the Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines. These experts concluded that the available evidence supports the following general guidelines regarding vaccinations:

1. Patients with MS should follow guidelines from the Centers for Disease Control and Prevention for immunizations. You can find this information at www.cdc.gov/vaccines/adults/index.html.
2. Vaccinations should be avoided during MS relapses, until patients have stabilized or have begun to improve from the relapse, which typically occurs around 4 to 6 weeks after it starts.
3. In general, flu, hepatitis B, and tetanus vaccines appear to be safe for people with MS.
4. The pneumococcal vaccine, which is given to prevent pneumonia caused by bacteria, should be considered for people with compromised pulmonary function, such as wheelchair-dependent or bed-bound patients or people with pulmonary diseases like asthma or chronic obstructive pulmonary disease (COPD).

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In regard to MS relapses, an additional systematic review of 51 studies was published in 2017, and found no association between relapses and vaccinations against hepatitis B virus, H1NI flu virus, or tetanus. However, there was some indication that vaccination against yellow fever might increase the risk of an MS relapse.

Vaccines and DMTs

Based on the evidence we have, this is the advice we give about vaccines to people with MS who are using DMTs:

1. Inactivated vaccines such as the yearly flu shot are generally considered safe for people with MS, including those who are taking an interferon medication (Avonex®, Betaseron®, Extavia®, Plegridy®, Rebif®), Aubagio®, Copaxone®, Gilenya®, Glatopa®, Lemtrada®, Novantrone®, Tecfidera®, or Tysabri®.
2. If you are on therapies that suppress the immune system, such as chronic corticosteroid therapy, you should consult your MS team before receiving any live-virus vaccines.

Vaccines for People with MS

Vaccine	Use in people with MS
Injectable seasonal flu	Considered safe
FluMist® nasal flu	Not recommended
Fluzone® high-dose flu	Not recommended because not studied, but probably okay for elderly people
Gardasil® (to prevent human papillomavirus [HPV])	Probably safe
Hepatitis B	Considered safe
Measles-Mumps-Rubella (MMR)	Probably safe in individuals not on immunosuppressant medications
Pneumovax® 23 and Prevnar® 13 (to prevent pneumonia)	Considered safe
Polio	Probably safe
Rabies	Probably safe; benefit likely outweighs any risks
Tetanus	Considered safe
Varivax® and ProQuad® (to prevent chicken pox)	Probably safe. Required prior to treatment with fingolimod (Gilenya®) and alemtuzumab (Lemtrada®) in patients who have not had chicken pox
Yellow fever	May not be safe; should not be used by individuals on immunosuppressant medications
Shingrix® vaccine (the newest vaccine to prevent shingles)	Considered safe for any adult who has had chicken pox but may cause flu-like side effects

Adapted from Williamson EML, Chahin S, Berger JR. Vaccines in multiple sclerosis. *Curr Neurol Neurosci Rep.* 2016; volume 16, page 36.

3. You should not receive a live-virus vaccine following a course of Lemtrada®.
4. If possible, you should receive non-live (inactive) vaccines 2-3 weeks before starting Ocrevus®. Live-attenuated or live vaccines are not recommended during treatment with Ocrevus®. All required immunizations should be discussed with your MS team.
5. If you are pregnant or planning to become pregnant, be sure to discuss the timing and safety of vaccinations with your obstetrician and MS teams.
6. MS experts have conflicting opinions about the risks of infection for a patient with MS if a close family member receives a live-virus vaccine. The family should discuss the best strategy for protecting all family members from infection with their MS team.

Your Take-Home Message

Patients with MS must protect themselves as much as possible from infections, which can trigger an MS relapse. Therefore, vaccines are often recommended to patients with MS to minimize the risk of infection, but it is important to discuss the safety of the vaccines and their effectiveness while you are on a DMT with your MS team. Non-live vaccines are routinely suggested to patients with MS. However, live or live-attenuated vaccines are usually not recommended due to a potential risk of MS relapses or disease progression. Further research is required to gather more data on the risks and benefits of different types of vaccines in people with MS, especially those who are on medications that deplete immune-system B cells or drugs that suppress the immune system.

Ask the Clinician

Q. I have progressive multiple sclerosis (MS) and my healthcare provider's office asked me for an advance directive. What is that and how do I get one?

–Muriel R. Gillick, MD

A. Advance directives are documents that enable you to specify the approach to medical care you would want if you became very sick and were not able to make healthcare decisions for yourself (otherwise known as incapacitated). Advance directives can also state who you want to make medical decisions on your behalf if you are incapacitated. Ideally, you complete an advance directive after having a conversation with your healthcare provider about your current state of health, your prognosis, and your values and preferences.

If you haven't considered how you would like your medical care to unfold if you have an advanced illness, you're not alone: the Centers for Disease Control and Prevention (CDC) report that 70% of Americans don't have advance directives. In fact, most people haven't even discussed their end-of-life wishes with their family, and many haven't thought about the final stage of life.

Advance care planning should be done before a health crisis strikes. And while it is important for adults of all ages, it is particularly important for those with a chronic disease like MS. It is difficult to think about getting sicker or dying. But without advance directives in place, you may not receive the care you want near the end of life and your caregivers, friends, relatives, and healthcare providers will be left to guess what you want.

Advance Directive Documents

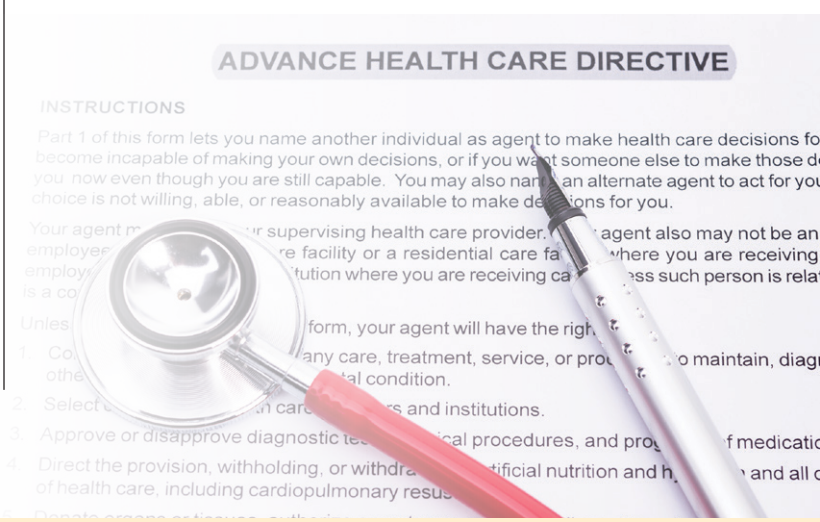
There are two main types of advance directives:

1. **A healthcare power of attorney.** This document names the person you wish to make healthcare decisions for you if you can't make them yourself. When choosing this person, you will want to name someone who will try to make the same medical decisions you would make if you could. The requirements for a healthcare power of attorney differ from state to state, but in general this person should be at least 18 years old and should not be your healthcare provider.
2. **A living will.** This document describes your specific desires for medical treatment. This can be very general—stating, for example, that you would want your medical care to focus exclusively on comfort or, alternatively, that you would want everything done to prolong your life. Or it can be very specific, stating whether you would want to be fed by a tube if you cannot take food by mouth, if you would want to be given antibiotics if you have an infection, if you would want cardiopulmonary resuscitation attempted should your heart or breathing stop, and if you would want to be kept alive by a mechanical ventilator should you be unable to breathe on your own.

Medical Orders

Related to advance directives are medical orders that specify in advance what kind of treatment a physician must provide (or may not provide) in particular circumstances. You and your healthcare provider need to decide together to draw up such an order. There are two main types of medical orders:

1. **Out-of-hospital DNR** (do not resuscitate), which informs emergency medical technicians that you do not want them to attempt cardiopulmonary resuscitation (CPR) in the event they find you without a heartbeat or not breathing. People who have a signed,



witnessed, out-of-hospital DNR form typically stick it on their refrigerator door, where it is easily accessible to ambulance personnel. Some people wear a MedicAlert® bracelet containing this information.

2. **Physician Orders for Life-Sustaining Treatment (POLST)** are for people who have a serious medical illness or are very frail and are at risk of dying within the next year. In some states, this may be called a MOST (medical orders for the scope of treatment) or POST (physician orders for scope of treatment) form. Depending on the state, this document must be signed by two witnesses and/or a notary public.

Important Details

You should keep a copy of each of these documents, once appropriately signed, at home and give copies to your healthcare power of attorney, family members, and your healthcare provider(s). It's also a good idea to put a card in your wallet that lists your healthcare power of attorney's name and contact information and the location of the original documents. (Some hospitals may require them.)

If you decide you would like to change these documents because your health, circumstances, or wishes have changed, they're not set in stone. You can void or rip up the old documents and create new ones.

Drawing up advance directives doesn't mean they will always be followed. Sometimes healthcare providers don't know the documents have been prepared, or emergency personnel may perform CPR because they are required by law to do so. The shift to electronic medical records is likely to improve the chances your wishes will be respected. Another good strategy is to use the smartphone app called "My Health Care Wishes," which was created by attorney Charles Sabatino of the American Bar Association. It allows you to upload all of your advance directive documents onto your phone and have them available to family members and healthcare providers as needed. Making sure that people involved with your medical care and your family have access to these documents will also help.

For More Information

Advance directives are a very complex area of medicine and law, so I suggest you research further as you go about the advance planning process. One resource is a Harvard Medical School Special Health Report *Advance Care Planning* (available at www.health.harvard.edu) that I wrote with Charles Sabatino, JD. (Versions of all of the forms listed above, by the way, can be found at www.health.harvard.edu/ADforms). I also write about end-of-life issues on my blog "Life in the End Zone," located at http://blog.drmurielgillick.com/. You might refer to these websites for more information as well:

- www.nia.nih.gov/health/caregiving/advance-care-planning
- www.cdc.gov/aging/pdf/advanced-care-planning-critical-issue-brief.pdf
- www.theconversationproject.org
- www.fivewishes.org
- www.caringinfo.org/AdvanceDirectives
- www.polst.org

— Muriel R. Gillick, MD
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MS AND OTHER ILLNESSES (Continued from page 11)

4. Does MS shorten life expectancy? Yes and no. The lifespan for people with MS is about 6 years less than for people in the general population, but the good news is that people with MS are living longer lives, reports Dr. Tremlett. "The average lifespan for a woman with MS was 78.5 years and the average lifespan for a man with MS was 74.3 years in our research, compared to 84 and 80 years in the general population. Once people developed MS, women were living about 50 years with MS, and men 40 years." The average person living with MS in Canada is now older, too: around 55 to 60 years in 2008, compared to 45 to 50 years in 1992. Findings have been similar in the US and Europe.

Living Longer and Better

The fact that people with MS are living longer than ever before and now have a greater opportunity to acquire comorbidities as they age makes it essential that the impact of these other diseases and their management are studied further, says Dr. Tremlett. It also means it's important for people with MS to manage their overall health along with their MS.

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