As Adults Age With MS, Should They Shed Their Meds?

The risks and benefits of immunosuppressive drugs for multiple sclerosis shift with age, but who should quit — and when?

Top: Neurologist Andrew Bouley (right) speaks with his patient Emily Wheeler while they look at her brain scans in his office in Massachusetts. Visual: Jodi Hilton for Undark

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IN JUNE 2021, 63-year-old Lisa Daurio was making the two-hour drive from her hometown of Pueblo, Colorado, to a doctor's appointment in Denver when she settled on a life-changing decision: She would tell her doctor she was ready to stop taking her weekly injections to treat her multiple sclerosis. Daurio was not cured, but her condition had remained stable for more than a decade. As she got older, her doctor had periodically asked if she wanted to consider halting her medication.

It's an unusual question in modern medicine: Clinicians don't typically ask people with arthritis, high cholesterol, diabetes, or other chronic conditions whether they'd like to stop taking their medication as they get older. But MS is an unusual disease, the result of immune cells attacking a

person's brain, optic nerves and spinal cord. The subsequent nerve injuries trigger burning pain, numbness, loss of balance, and a range of other symptoms. These hallmark immune assaults and symptoms flare up sporadically in younger adults and, for some people, seem to quiet down as they age into their 50s and beyond.

Still, Daurio's decision to stop wasn't straightforward. Her MS symptoms began when she was in her late 30s, with a sense of overwhelming fatigue, a numbness in her legs, and a "feeling of fire ants" that ran "from the back of my neck around the front of my face," she said. She was diagnosed with MS in 2003, when her entire left side went numb, and she thought she was having a stroke. The weekly injections had kept all of those symptoms at bay for more than a decade. When her doctor broached the idea of stopping them, Daurio's reaction was "it's working, let's not mess with what's not broken," she said.

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Staying on her medication wasn't always easy. For about 10 years, every dose made her feel like she had the flu. After each shot, she spent two days on Tylenol and a steroid named prednisone to cope with the side effects. But Daurio stuck with the regimen because the injection seemed to help; she

had not had a single relapse since 2009, and periodic MRI scans showed no new signs of immune attacks on her brain.

Daurio's decision to quit the injections was based in part on the results of a recent clinical trial she participated in that found no significant increase in relapses when people over the age of 55 stopped taking their MS drugs, which can range from injections to infusions to pills. That study, known as the DISCO-MS study, is among the latest efforts in a long history of researchers trying to understand MS and apply scientific advances to help those living with the disease. But the DISCO-MS study did not reveal clear benefits to either continuing or discontinuing medications. And although Daurio has not suffered any relapses since she last took her injections, not everyone shares her experience.

That's par for the course with a disease that affects people in many different ways. Although studies suggest that people still view MS — wrongly — as a deeply debilitating condition that makes the average lifestyle of a working adult difficult or impossible to lead, in reality, people with multiple sclerosis experience a sprawling variety of symptoms, ranging from near invisible to devastating, depending partly on the form of their immune reaction. Some end up needing to use a wheelchair within a decade of a diagnosis; others experience almost no disability; still others range between these two extremes.

“We do still have this idea of multiple sclerosis as a person in a wheelchair,” said stem cell biologist Valentina Fossati of the New York Stem Cell Foundation. “That’s not true.”

> *When her doctor initially broached the idea of stopping them, Daurio’s reaction was “it’s working, let’s not mess with what’s not broken.”*

The reality of living with MS changed dramatically in the 90s, Fossati says, when the first drugs to treat the disease entered clinics. Now, after hundreds of scientific studies and the approvals of more than 25 drugs, clinicians and researchers know drastically more about MS — and how to treat it.

Much of that progress has hinged on the participation of several thousands of people with MS, including Daurio, in clinical studies over the last 30 or so years. But people with MS have not just volunteered to help advance research — they have also had to consider changes to their own daily rhythms when science drops a new beat of evidence. People of Daurio’s generation, one of the first to have treatments at all, continue to navigate unknown scientific frontiers as they age. What has it meant to spend decades of their lives on the cutting edge of scientific discovery?

Little is known about how aging alters the benefits and risks of the medications that Daurio and others rely on, in part because these treatments were mostly tested in people under the age of 55 before they were approved. And researchers are still working to understand how the immune system changes with age.

Across several studies, researchers have found that getting older seemed to reduce the risk of an immune flare-up and relapse in MS symptoms and raise the risk of troublesome side effects from MS drugs. Still, when it comes to treatment, "it is very unclear what to do with people as they age," said neurologist Andrew Bouley, who is co-director of The Elliot Lewis Center for Multiple Sclerosis Care in Massachusetts. Clinicians "have a very good understanding of what to do" when people with MS are in their 50s and younger, he said. "Once you hit 60s and 70s, I think this is all gray area."

MULTIPLE SCLEROSIS WAS first defined in the late 19th century, but it was roughly a century later when researchers homed in on its immune origins. The condition's trigger is still a mystery, but it is known to be an autoimmune disorder: For unknown reasons, the body's immune system begins to attack the central nervous system. Immune cells cross the blood-brain barrier and activate resident immune cells in the brain and spinal cord to strip the fatty

myelin sheath that protects nerve fibers. The symptoms a person might experience depend on what region of the spinal cord or brain is attacked and how severely.

In its most common form, known as relapsing-remitting multiple sclerosis, the disease manifests as sporadic, repeated flare-ups, with each recurrence attacking the nervous system and potentially creating new lesions. During a flare-up, a person's symptoms might cause pain, difficulty moving, and loss of vision or balance. Then immune activity quiets down, symptoms abate, and — in younger people — life often returns to normal, although attacks may cause lingering nerve damage. "Things don't always get a hundred percent better after an attack," said Jennifer Graves, a neurologist at the University of California, San Diego, "but there is improvement."

In 1993, the FDA approved interferon beta-1b, the first drug shown to reduce the number of immune attacks that people with MS experienced. People who took the injection at its highest dose in the study had about a 34 percent (https://www.neurology.org/doi/abs/10.1212/WNL.43.4.655) lower rate of relapse than those who received only a placebo. Three years later, the agency approved a second injectable drug named Avonex, or interferon beta-1a, which was among the first medications to reduce the frequency of disease relapses, new

immune attacks on the brain and spine, and the overall decline caused by these repeated cycles of flare-ups.

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The same year that Avonex was approved, then-37-year-old Emily Wheeler was diagnosed with relapsing-remitting multiple sclerosis. Wheeler loved to hike and bike and could go months feeling perfectly normal. Then her disease would flare up, and she would find herself unable to move off her couch, needing to take steroids to suppress her symptoms enough to be able to walk. The many unknowns packaged into her diagnosis were terrifying, she said.

Shortly after her diagnosis, Wheeler was prescribed an immunosuppressive medication that was commonly given to liver transplant recipients but also seemed to help people with MS. She later switched to Avonex, shortly after it was approved. The treatment was available only as a weekly intramuscular injection. Each dose left her feeling

like she had the flu, a side effect she countered with Tylenol, and the injections themselves were unpleasant. “I really didn’t like giving myself the shots,” Wheeler said, and she was unsure if the medicines really made a difference, since — even before she began treatments — she could go months without a flareup.

The injections and their flu-like side effects frustrated Wheeler. In 2009, she enrolled in a clinical trial for a new oral pill drug named Tecfidera, then stayed on the drug after it was approved.

Tecfidera is one of dozens of now-approved drugs that prevent relapses by suppressing the immune system and thus blocking attacks on the brain and spine. None of them are a cure, but people who take these medications can experience fewer relapses than they would without the drugs. People who are diagnosed in their 30s may remain on the treatments for years, their disease neither improving nor worsening.

At age 37, Emily Wheeler was diagnosed with relapsing-remitting multiple sclerosis. She has taken several drugs to treat the illness over the years. When she was in her early 60s, Wheeler stopped taking her medication, but experienced a relapse two months later. *Visual: Jodi Hilton for Undark*

“Stable to me is a good thing,” said Bouley, from the Elliot Lewis Center. “Our goal, and I try to set this expectation when I start someone on a therapy, is

not to make people improve, but to keep them from getting worse. So, if someone's stable, well, I would argue that means we're winning."

In 2018, when she was in her early 60s, Wheeler — who is a patient of Bouley's — wondered: What if she stopped? Addressing her MS had always "felt a little more like magic than science," she said. "Usually when you're sick, if you take a drug, then you get better." But managing her MS felt more imprecise. "You take the drug and then you go four months without a flare-up instead of — instead of what? You never know," she said.

She stopped without checking with her doctor at the time. Two months later, she had her first relapse in years. "I called my doctor, and I confessed," Wheeler said. "She absolved me and then we went back to the Tecfidera."

MODERN MS DRUGS can keep people relatively free of relapses for years. But getting older can shift that equilibrium. Even in the absence of MS, aging is linked to a loss of muscle strength, weakened immune response, decreased resilience, and increased susceptibility to respiratory infections and other illnesses. "One thing that youth and kids do really well is recover from injury, whether it's MS or stroke or a car accident," Graves said. "We generally

appreciate that aspect of aging, that we just bounce back less easily from various types of bodily injury as we age."

One reason for this decline is a gradual shushing of immune responses, a process known as immunosenescence. With age, the immune system is generally slower and less responsive to vaccines and infections — and to whatever inflammatory trigger causes the immune surge responsible for MS flares. Since relapses require large, robust immune responses to attack entirely new areas of the central nervous system, they may become less frequent with age, Graves said.

Immunosenescence doesn't spell respite from all autoimmune conditions. Some, such as rheumatoid arthritis and lupus, can worsen with age. MS can shift toward a different form of the disease, one where the cycle of relapse and recovery yields to a more progressive, permanent disability. Although new MRI lesions and clinical flare-ups decrease with age, MS symptoms such as muscle weakness and loss of balance worsen and persist for longer spells, Bouley explained. Although relapses become rarer, the disease may worsen. "It's really complicated," he said. "MS does get worse. There is a progressive component to it, but the amount of relapses and new inflammation that we see on the MRIs, that does not get worse."

Clinicians define this slow increase in disability as secondary progressive multiple sclerosis, distinct from the relapsing-remitting form common in younger adults. But these classifications belie what, in actuality, is still a relatively immature understanding of how the disease changes with age, said New York-based stem cell biologist Fossati.

Stem cell biologist Valentina Fossati prepares microscope slides containing sections of 3D human models of the brain, with neurons and resident immune cells, for a study on Alzheimer's disease. Fossati, who was diagnosed with multiple sclerosis at age 30, has also studied MS using stem cell-based models. *Visual: Samwan Rob, The New York Stem Cell Foundation*

In laboratory studies using stem cells, Fossati has found that immune cells living in the central nervous system may explain the disease's different forms. Other researchers have developed similar findings using animal models. The secondary progressive form of MS seems to be marked not by external immune attacks that breach the blood-brain barrier to strip nerve fibers of protective myelin, but by the activation of immune cells resident in the brain, which seem to spur scar formation and botched repairs of damaged myelin. But precisely what causes the immune system to switch in this way is unclear, and clinicians still struggle to pinpoint the transition from relapsing-remitting MS to the secondary progressive form with tests and biomarkers.

Diagnostics are not the only hurdle. Most MS drugs were tested in people below the age of 55 and are generally less effective against progression. "When

we say it's less effective, what we're really saying is that it doesn't stop the disability progression in someone who's not having relapses," said Le Hua, neurologist at the Cleveland Clinic Lou Ruvo Center for Brain Health. "It's not that our medications don't work in an older person who's having relapses. It doesn't work well in a person where their primary disability is not being driven by the external immune system."

To Fossati, figuring out what drives these changes with age is not just a scientific quest. She herself was diagnosed with MS shortly after her 30th birthday, and she grew up surrounded by the reality of living with progressive forms of MS: Her parents volunteered with the local MS community in her hometown, and her mother's best friend, who had a more severe, faster-progressing form of MS, had used a wheelchair since the 1970s.

Fossati's personal journey with the condition began with a burning sensation that ran down her right leg. Nothing eased the strange pain. She couldn't feel the ice that a friend placed on her leg. Another friend suggested she get an MRI as a precaution before an upcoming vacation to the Bahamas. The scan led her doctor to recommend further tests, which revealed multiple MS lesions on her brain and one on her spinal cord. Fossati feared for her "dreams of becoming a scientist, of having kids," she said. "At

the very beginning I was like — that's it, I'm going to be in a wheelchair and I'm going to spend the rest of my life alone."

Fossati was diagnosed with relapsing-remitting MS, but her work and her body are constant reminders of the uncertainty that lies ahead. "I'm honestly very scared about potentially now reaching the 50s in four years," she said.

EXISTING DRUGS ALSO appear to pose greater risks for older MS patients. Most MS drugs reduce flareups by tamping down the immune response. With age, this potentially risks further suppressing an already-tapering immune system, so people on treatments are at greater risk of infections and are less protected by vaccines. The drugs come with other side effects — including a higher risk of a rare, brain-damaging condition — and they may also spike the risk of cancers, in part because they deplete immune cells that identify and eliminate precancerous cells. In a 2021 analysis (https://pubmed.ncbi.nlm.nih.gov/33104449/), researchers evaluated data from 45 clinical trials of existing MS drugs and found that people who used some of these drugs had a higher rate of tumors, especially after the age of 45, compared to control groups — although the effect was just behold the

threshold to be considered statistically significant (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/statistically-significant).

As people age, they're also more likely to be on medications to treat diabetes, heart disease, and other conditions. Some MS drugs can raise blood pressure and shouldn't be taken with certain other prescriptions, said John Corboy, a professor of neurology at the University of Colorado Anschutz Medical Campus.

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Corboy is one of many clinicians who observed that his patients had fewer relapses or new signs of disease on their MRIs as they grew older. The repeated observations and potential for higher risk from the drugs led him and others to launch the DISCO-MS study (https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(23)00154-0/abstract), the first randomized controlled trial to systematically weigh the pros and cons of discontinuing MS treatments in older patients with stable disease. Over a two-year period, the research team compared how people 55 and older with MS fared with and without treatment. They found that disease outcomes in the group that stopped drugs did not appear significantly worse than for the group that continued. Side effects, such as upper respiratory tract infections, occurred at

similar rates for both groups, but they were slightly more severe in the group that discontinued treatment. And the discontinuation group had a slightly higher risk of new brain lesions, though these lesions were not associated with new or worsening symptoms, Corboy explained in an email.

One significant difference between the groups was how comfortable they felt, Corboy said: “Patients who went off-drug were more satisfied with their treatment assignment than the people that stayed on-drug.”

The bottom line, however, was that the study revealed little about the benefits of stopping treatment: Discontinuing was, essentially, no worse than continuing; but it was no better either. The real question — Should clinicians prescribe MS medications differently as people age? — remained unanswered.

“Does it change our current practice?” asked University of Pittsburgh neurologist Zongqi Xia, one investigator on the DISCO-MS trial. “The answer is no, not greatly.”

“It didn’t swing the pendulum one way or the other in the dramatic fashion that we hoped,” Xia added. Because the trial did little to tip the scales, patients and clinicians have been left to navigate the discussion on their own, albeit with data from one more study to guide their choices.

People with MS are often reluctant to let go of the treatments that have helped them achieve decades of health. In a survey (https://journals.sagepub.com/doi/abs/10.1177/135245851986731 of people on MS medications, Corboy said he and his colleagues found that about two-thirds of the respondents were uninterested in discontinuing drugs, and only about 12 percent said they would consider or strongly consider going off treatment, even for a trial period.

Daurio spent years mulling her own choice about MS treatments before she made the decision to discontinue them in 2021. Four years earlier, she signed up to participate in the DISCO-MS trial — her way of paying forward the good deeds that previous trial participants had done for people like her. “To have the drugs that I had, somebody had to be willing to go through studies,” she said. “I felt if I was able to do that for people that come after me, I would be grateful.”

Daurio was randomly chosen to participate in the control group and thus remained on her injections through the trial, but she chose to stop after participating in a follow-up study.

Wheeler, now 67, has also considered the idea of stopping her MS treatments since her doctor broached the idea about two years ago. But she isn't interested. She has not experienced a relapse for several years now. But when she had them, Wheeler felt off-balance, with an unsteady gait and wooden feeling in her legs. "The older I get, the more that is the case all the time," she said. "I don't want to speed up the aging process any more than I have to."

To her, staying on medicines is a way of holding on to the things that bring her joy: "I have a walk that I really like to do, I'm a bird watcher, and I like to swim. And if I couldn't do any of those things, I would be a lot less happy."

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The DISCO-MS study and subsequent studies offer a breadcrumb trail of clues about which patients' disease will progress, and who may be able to safely discontinue their treatments. Biological sex seems to play a part in whose disease will progress: Women

seem to experience less disability than men. Biological age appears to matter too (https://pmc.ncbi.nlm.nih.gov/articles/PMC10843499/), though the related research metrics have yet to be translated into practical clinical tests.

Future trials conducted among people aged 65 and older might yield more definitive answers about a course of treatment, Bouley suggested. He remembers discussions about stopping therapy at the age of 55 when he was doing his medical training 10 years or so ago, but the more appropriate transition age may prove to be in the 60s or at 70, he suspects. "Older individuals are oftentimes healthier, including our MS patients because they're doing better now that they're on these therapies as well," he said. "I feel like my timeline has shifted."

A growing recognition that the course of MS is not uniform for every person with the disease has meant that every person aging with the disease is, in effect, balancing their own risk-benefit equation. Each person must navigate their own decisions with their doctor, Fossati said.

Fossati added that she would not hesitate to explore weaning off MS drugs with her doctor, if that becomes an option for her. Navigating an active career that involves attending conferences, traveling, and other responsibilities has been challenging because of the immunosuppressive treatment she

takes. But she understands that the balance of risk and benefit may be different for someone who is homebound after retirement.

As people age, their health risks and bodies change too, she said, “and so why not also the regimen, the medications that you take?”

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