

When sleep disorders presage something more serious

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Early one morning, while checking on a slumbering patient at the Center for Sleep Medicine, Erik St. Louis, M.D., noticed something peculiar. The patient, a woman in her early 60's, had started running beneath her

bedsheets. As her eyelids fluttered, her legs kicked into gear, slowly at first but then rapidly picking up the pace, propelling herself along a road only she could see. After sprinting for about 30 seconds, she abruptly stopped and opened her eyes. It wasn't the way Dr. St. Louis had expected someone with sleep apnea to behave.

Later, when he met her in his office, he asked what had happened. "Well, I have these crazy dreams sometimes," she responded. "I was dreaming that there were two men chasing me. I could see a getaway car that was going to help me escape—I could see the taillights and it was pulling away slowly so I ran faster and faster to catch up with it. Finally, when I was just about to jump in the car, I woke up."

Dr. St. Louis, a neurologist and sleep medicine physician at Mayo Clinic, had heard different versions of the same story countless times before. Acting out dreams while asleep is the main manifestation of [REM \(rapid eye movement\) sleep behavior disorder or RBD](#), a parasomnia that he and his colleagues at Mayo Clinic have been treating for decades. They have found that in addition to the potential for injury to patients and their bed partners, RBD could be an early sign of neurodegenerative diseases like Parkinson's disease.

Thought to affect only about 1% of the general population, RBD is prevalent enough that Dr. St. Louis sometimes identifies it while assessing a patient for another, more common sleep condition. "It can be completely unexpected and a revelation to both the patient and me," he says.

A team of Mayo Clinic sleep researchers are helping to lead an ambitious effort to gather as much data about RBD as possible.

"The end game is to understand the natural history of the disorder well enough that we can do a neuroprotective treatment trial of a medication

or intervention that can prevent Parkinson's disease or dementia from developing in the future," says Dr. St. Louis.

Bad dreams

In REM sleep behavior disorder, your brain cycles through REM sleep many times during the night, each cycle getting longer and longer until, by morning, it adds up to about a quarter of a night's sleep. During REM sleep, your eyes move rapidly beneath your eyelids, your dreams turn more vivid and intense, and most of your muscles are paralyzed.

"In an evolutionary sense, that paralysis is a good thing. Otherwise, every time we dreamt we were being chased by a tiger we would jump out of bed and run down the hall, which certainly wouldn't be healthy," says Mayo neurologist and sleep medicine physician Michael Silber, M.B., Ch.B.

Patients with REM sleep behavior disorder, however, lose that paralysis, and therefore seem to act out their dreams. As a result, they can pass the night singing, shouting, screaming, punching, jumping, kicking and flailing their arms, [injuring themselves](#) and others, sometimes seriously. One patient dove across the room to catch an imaginary football and hit his head on a dresser. Another pulled out a gun and fired it down the hall at attackers that weren't there. One mistook his wife for a bear and began strangling her. Another stood up on his mattress and pantomimed skiing, jumping over a pretend mogul and spraining his ankle when he hit the floor.

Such bizarre episodes of dream enactment were not recognized as a medical disorder until 1986. Over a decade later, Dr. Silber, along with neurologist Bradley Boeve, M.D., neuropsychologist Tanis Ferman, Ph.D. and others at Mayo published a series of studies showing that RBD can be [more than just a nighttime nuisance](#).

The team found that approximately 50% to 80% of people with RBD go on to develop a neurodegenerative disorder, specifically one in which abnormal deposits of a protein called alpha-synuclein accumulate in the brain. The [synucleinopathies](#), as these disorders are known, include Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Toxic clumps of alpha-synuclein appear to damage parts of the brain stem responsible for immobilizing our muscles while we sleep before moving on to other regions controlling more overt daytime activities.

"Our work has shown that RBD develops years and often decades before the development of parkinsonism or cognitive impairment," says Dr. Ferman. "RBD provides a potential window for the early detection of the synucleinopathies and for future therapies that specifically target the proteins responsible for the neurodegeneration."

Charting the disease

Researchers at Mayo Clinic are helping to lead the NAPS Consortium, a study that is laying the groundwork for future clinical trials of protective treatments. The study is enrolling patients with RBD at nine different sites across North America and putting them through a battery of tests—including brain imaging, muscle activity, blood tests, genetic screens, neuropsychological evaluation and polysomnography or sleep studies.

"We just need to cast a wide net before we can see which tests are the best predictors of the future," says Dr. Boeve, who is co-PI of NAPS.

The team plans to follow more than 300 patients over time, mapping various aspects of their condition as some go on to develop a more obvious neurodegenerative illness. With that data in hand, they will be better prepared to identify those patients who are at imminent risk and

assess the impact of various treatments currently under development at pharmaceutical companies.

The researchers now have a few new biomarkers at their disposal that enable them to track the condition even more closely. They can detect and measure alpha-synuclein in cerebrospinal fluid from a spinal tap, as well as in small nerve fibers from a skin biopsy. And they recently got a grant from the American Brain Foundation to develop a blood-based biomarker to do the same.

"I always liken this to high cholesterol," says Dr. Boeve. "Now we have all these medications that lower cholesterol and decrease the risk of heart attack and stroke. So can we reduce the risks in someone with RBD, to delay the onset or prevent development of future illness?"

The future

Unfortunately, researchers have yet to discover an intervention that can completely alter the trajectory of patients destined to develop Parkinson's or a similar neurodegenerative disorder. Which, Dr. Silber explains, presents an ethical conundrum. "Should we tell our patients what might happen in the future, when we can't do anything to prevent it from happening?" he says.

Recently, the Mayo Clinic research team [surveyed 113 RBD patients](#) to see what they thought. More than 90% of respondents said they would want to know they were at risk. The patients felt that such prognostic information was important to discuss with their family and friends and could help them plan for the future. But when the researchers asked how that knowledge made them feel, a high percentage of patients said it caused them distress and anxiety.

"We have to handle that anxiety," says Dr. Silber. "I spend a lot of time

counseling patients, telling them please don't let this dominate your life." It may be many years or even decades before a neurodegenerative disease manifests, and by no means all RBD patients will develop one in their lifetime. He also notes that if patients know they are at risk, they can participate in [clinical research](#), an option that might not have been available had they stayed in the dark.

Mayo researchers hope to develop more options to offer patients in the future to prevent neurodegeneration from progressing. One avenue they are exploring involves bioelectronic devices, a type of medical device that uses electronic signals to treat or diagnose disease. For example, [transcranial magnetic stimulation](#) (TMS), a non-invasive brain stimulation treatment which harnesses magnetic pulses to stimulate nerve cells in the brain, is now a standard treatment for depression. Mayo Clinic psychiatrist Maria Lapid, M.D., is testing whether TMS can alleviate mild [cognitive impairment](#); Dr. Boeve thinks a similar approach could be applied to synucleinopathies.

Similarly, Dr. Boeve would like to see bioelectronic devices that could monitor and diagnose RBD as patients act out their dreams in the comfort of their own homes.

"It is a tricky disorder to diagnose," he says, "because if you don't know what you're looking for, you'll miss it."

Provided by Mayo Clinic

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