



The Parkinson's *predicament*

THE SIDE EFFECTS
OF TREATING THIS
DEVASTATING DISEASE
CAN BE ALMOST
AS AWFUL AS THE
ILLNESS ITSELF.
ONE BINGHAMTON
RESEARCHER HOPES
TO CHANGE THAT.



Christopher Bishop

Christopher Bishop has a novel theory about how to suppress the involuntary movements associated with Parkinson's disease. His idea could revolutionize the way patients respond to the drug that has been the gold standard in treating the disease for more than 50 years and lead to vast improvements in the quality of life for the roughly 1 million Americans who suffer from Parkinson's.



THE SITUATION IS AN INCREASINGLY URGENT MEDICAL CONCERN; 50,000 MORE AMERICANS ARE DIAGNOSED WITH PARKINSON'S EACH YEAR.

Parkinson's disease patients have trouble with movement. They move slowly. They have rigidity in their limbs. They have balance problems and tremors.

These cardinal symptoms are a result of a deficit of dopamine in the brain.

Dopamine is a neurotransmitter that's essential for movement; it also plays an important role in behavior, cognition and sleep.

In Parkinson's patients, neurons that make dopamine die. Scientists still aren't sure why; genetic factors are believed to play only a small role.

This deficit of dopamine can be reversed with treatment using a compound called L-DOPA.

The brain converts L-DOPA into dopamine, which is why it's an effective replacement therapy for patients. And for five to 10 years, this treatment works well.

"The problem is that Parkinson's is a progressive disease," said Bishop, assistant professor of psychology at Binghamton University. "You lose more and more of these neurons as time goes on, so therapeutically, doses of L-DOPA must increase."

Many patients suffer troubling side effects as the dosage increases.

“By year 10,” Bishop said, “as many as 90 percent of patients will start to suffer from motor fluctuations and something called L-DOPA-induced dyskinesia. So you go from a state of no treatment where you’re not moving well, to a state where the drug is working well and you’re moving fluidly, to a point where L-DOPA doses are very high and you’re producing these abnormal, involuntary movements.”

Think of the actor Michael J. Fox’s recent television appearances. The excessive movements he displays aren’t a result of his Parkinson’s disease, but rather a symptom of the L-DOPA therapy.

“It’s this inability to suppress movement that’s a real problem for patients later on in the disease’s progression,” Bishop said.

And patients can’t simply stop taking L-DOPA, Bishop said. If they do, they face a nearly “frozen” life with incredibly limited ability to move.

It’s unusual that there hasn’t been a change in the primary treatment for Parkinson’s in five decades, Bishop said. In that time, there have been huge advancements in the ways other neurologic disorders are treated.

With Parkinson’s, there are still a number of big unanswered questions. The cause of the disease is one; how dyskinesia develops is another.

Bishop and colleagues at Wayne State University’s medical school and the Veterans Administration hospital in Chicago hope to find a way to reduce dyskinesia and suppress these movements.

“We’re asking, ‘Is dyskinesia abnormal learning?’ There are parts of the brain that allow us to store memories. And that involves laying down new neuronal pathways that become permanent. You can now go and retrieve that information.

It’s not always at the forefront of your mind, but it’s something you can get to if you need to,” Bishop said. “In the same way, your ability to produce a movement is a memory. It’s a motor memory, but it’s a memory nonetheless.

“We are beginning to believe that dyskinesia is actually the inability to suppress motor memories as a result of the drug’s stimulation. These abnormal movements may be an expression of motor memories that can’t be shut down.”

One possible treatment relates to glutamate, a neurotransmitter in the brain that can play a role in these memory processes, helping to lay down new pathways for motor memories.

Bishop has developed a way to look at dyskinesia as it’s occurring and measure glutamate levels in different parts of the brain. “That is a huge leap forward,” he said, “because now we can make an association between the behavior and the glutamate levels. And we’re doing it in a very specific area of the brain. It’s a very powerful technique.”

Kathy Steece-Collier, an associate professor in the Department of Neurology at the University of Cincinnati, said “surprisingly little” research effort to date has taken the direction Bishop is pursuing.

“Chris’ approach has been to delve into novel molecular mechanisms,” she said. “These mechanisms have a strong potential to provide insight into new clinical approaches that could prolong therapeutic treatment and lessen side effects associated with L-DOPA therapy in Parkinson’s disease.”

In 2008, Bishop and his team received a \$1.33 million, five-year grant from the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health. The funding will allow Bishop and his team to study serotonin compounds that reduce glutamate following L-DOPA



treatment. Bishop hopes to find out how these compounds work — and what dyskinesia really is.

Early experimentation has supported Bishop’s theories, showing a reduction in dyskinesia as the serotonin compound is administered.

“Dr. Bishop’s research is important because he has focused on a brain chemical transmission system that may represent a new therapeutic target for treatment of L-DOPA-induced dyskinesias,” said Beth-Anne Sieber, a program director at the National Institute of Neurological Disorders and Stroke. “His NINDS-funded studies suggest that activation of



ABOUT PARKINSON'S DISEASE



Parkinson's disease belongs to a group of conditions called motor-system disorders, which are the result of the loss of dopamine-producing brain cells. The four primary symptoms of Parkinson's are tremor, or trembling in hands, arms, legs, jaw and face; rigidity, or stiffness of the limbs and trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance and coordination.

a receptor for the neurotransmitter serotonin can block overactive brain signals and dampen involuntary movements."

Bishop said he believes L-DOPA treatment will remain in the mix of therapies, even if other advances such as stem-cell transplants advance to a point where they can be used regularly.

The situation is an increasingly urgent medical concern; 50,000 more Americans are diagnosed with Parkinson's each year. "That's only going to increase as our population ages," Bishop said. "This is not something that's going away." ■

— Rachel Coker

Parkinson's usually affects people over the age of 50. Early symptoms are subtle and occur gradually. The diagnosis is based on medical history and a neurological examination. The disease can be difficult to diagnose accurately. Roughly 50,000 Americans are diagnosed with Parkinson's every year.

There are many theories about the cause of Parkinson's disease, but none has ever been proved. At present, there is no cure for Parkinson's, but medications provide many patients dramatic relief from the symptoms.

The disease is both chronic, meaning it persists over a long period of time, and progressive, meaning its symptoms grow worse over time. Although some people become severely disabled, others experience only minor motor disruptions.

Source: National Institute of Neurological Disorders and Stroke