

NINDS Contributions to Approved Therapies

NINDS invests in and conducts research across the spectrum of neuroscience and neurology research, from basic studies on fundamental biological mechanisms, to clinical trials to test new treatments in patients. Here, we describe the path leading to the development and approval of one therapy for a neurological disorder, and we highlight contributions enabled by NINDS and NIH support.

Deep Brain Stimulation (DBS) for the Treatment of Parkinson's Disease and Other Movement Disorders

Overview

Parkinson's disease (PD) is a neurodegenerative disorder that leads to resting tremor, rigidity, slowness of movement, and postural instability. These symptoms are caused by degeneration of neurons in the substantia nigra pars compacta (SNc), one of a group of brain structures known as the basal ganglia and part of a circuit crucial for coordinating purposeful movement. This circuit relies on the chemical messenger (or neurotransmitter) dopamine, which is produced by SNc neurons. As PD progresses and these neurons are lost, reduced dopamine results in abnormal circuit activity and motor symptoms.

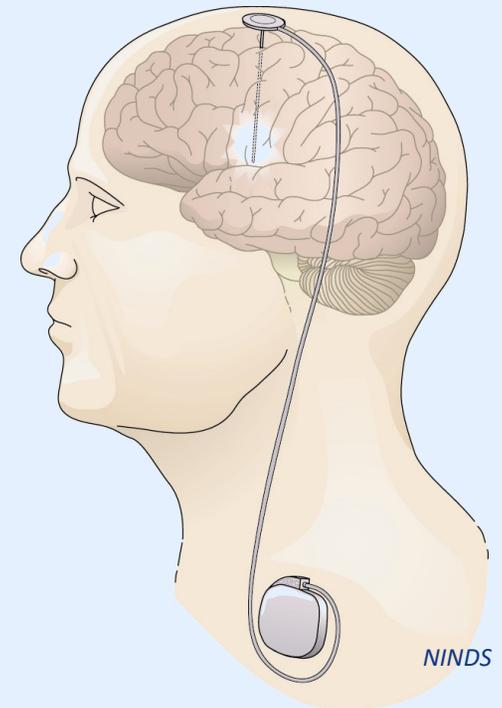
The molecular precursor to dopamine, L-DOPA (or levodopa), is used to treat PD. However, people in later stages of the disease experience "off" periods when this medication does not work well. L-DOPA treatment also can trigger uncontrolled involuntary movement, a condition called dyskinesia. Deep brain stimulation (DBS) can offer symptomatic relief in later stages of PD and may reduce requirements for L-DOPA treatment and exposure to its side effects. DBS also is used to treat other

movement disorders, including essential tremor, which causes involuntary shaking (often in the hands) that worsens during movement, and dystonia, which causes involuntary muscle contractions and slow, repetitive movements or abnormal postures.

DBS involves a device similar to a cardiac pacemaker that sends electrical signals through wire electrodes implanted in the brain. For movement disorders, electrode locations include brain structures important for motor control. Rigidity, tremor, and dopamine-induced dyskinesia in people with PD are treated with stimulation in the subthalamic nucleus (STN) or the internal segment of the globus pallidus (GPI) (FDA approval, 2002). These same sites are stimulated for the treatment of dystonia (granted a special FDA approval called a Humanitarian Device Exemption (HDE), in 2003). DBS in the ventral intermediate nucleus of the thalamus (VIM) is used to treat essential tremor and tremor as a primary symptom of PD (FDA approval, 1997).

Basic neuroscience research, supported by NINDS and NIH to understand neural circuits involved in motor control and how they are

affected by PD, was essential to the development and clinical application of DBS. NINDS, along with the Department of Veterans Affairs and industry, also sponsored a major clinical trial that showed DBS for PD was superior to L-DOPA treatment alone.



Learn more at: <https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies>

DBS for Parkinson's Disease and Other Movement Disorders Development Timeline



Albert and Mary Lasker Foundation

Benabid and DeLong share the 2014 Lasker-DeBakey Clinical Medical Research Award for their roles in developing DBS of the STN for the treatment of PD.

DeLong and NINDS-funded colleagues propose a model of basal ganglia circuit organization, with parallel, functionally segregated circuits involved in movement and other complex functions.

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1984-1986

1979-1983

1971-1974

NIH intramural scientist Mahlon DeLong conducts foundational research on how the basal ganglia controls movement. He and colleagues describe activity in the basal ganglia, cerebellum, and motor cortex during the control of movement.

NIH

1967-1973

Stimulation in the spinal cord and thalamus is used to treat chronic pain, employing modified cardiac pacemaker devices.

NIH NINDS

1950

Treatments for various movement and psychiatric disorders involve surgical lesions to brain areas, using electrical stimulation in awake patients to identify targets.

A large NINDS-funded clinical trial in coordination with the Department of Veterans Affairs shows that DBS is superior to L-DOPA, the best medical therapy at the time, for decreasing PD symptoms.

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2009

The FDA expands indications for DBS, approving its use in the STN or GPI in advanced PD and allowing its use for dystonia.

2002-2003

Benabid and colleagues use DBS to inactivate the STN in patients with PD. They report improvement in tremor, rigidity, slowed or reduced movement, and gait. Larger clinical trials to assess DBS in the STN and GPI follow.

1997

The FDA approves VIM-DBS for essential tremor and severe tremor in PD.

1995-2001

1994

Swiss neurosurgeons Siegfried and Lippitz report that chronic stimulation in the internal segment of the globus pallidus (GPI) improved symptoms in three patients with advanced PD.

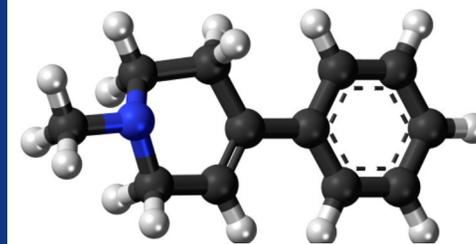
1990-1991

DeLong and others find that inactivating the STN with lesions or high frequency stimulation reduces major motor symptoms of PD in MPTP-treated monkeys.

NIH NINDS

1987-1991

French neurosurgeon and scientist Alim-Louis Benabid reports that DBS in the ventral intermediate nucleus of the thalamus (VIM) can reversibly decrease tremors in patients with PD.



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A case report from NIH scientists describes PD-like symptoms after use of an illicit drug. Studies of more cases by William Langston identify the compound MPTP as the cause. The findings lead to an animal model for PD.

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