

Michael J. Fox Foundation Impact in: Dyskinesia

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Executive Summary

On the heels of recent announcements by two companies working toward better treatments for dyskinesia, The Michael J. Fox Foundation offers this overview of some of the most promising research currently under way to alleviate this debilitating complication of PD treatment.

Dyskinesia is a top priority for our Foundation because of its significant negative impact on patients' quality of life. Similar to our work in other high-priority research areas, the Foundation takes a portfolio approach to driving new treatments for dyskinesia. We are working to identify and push forward the most promising drug targets while simultaneously creating infrastructure that will enable efficient and conclusive clinical trials of future drug candidates. The goal, as always, is to accelerate the progress of potential new treatments toward pharmacy shelves and into patients' hands.

Dyskinesia: A Disabling Aspect of Life with Parkinson's Disease

Dyskinesia refers to the excessive and uncontrollable movements that are a complication/side effect of long-term dopamine replacement therapy in patients with Parkinson's disease. Dyskinesia is a harrowing problem for people with Parkinson's disease, who report that it is one of the most difficult aspects of Parkinson's to manage.

Because they fear developing dyskinesia, many patients wait as long as possible to begin using the drug levodopa, our "gold-standard" treatment for relieving the stiffness, tremors and rigidity that are the cardinal features of PD. Even after starting the medicine, many limit the dosage to reduce the risk of dyskinesia. Those who do develop dyskinesia often need to reduce their levodopa dose and therefore settle for a sub-optimal benefit from the best medical therapy available for their disease. There is no therapy approved by the U.S. Food and Drug Administration (FDA) to treat dyskinesia.

Overview of Dyskinesia Therapies in Development Funded by MJFF

In recent years, modifying circuitry in an area of the brain called the basal ganglia has emerged as a promising strategy to alleviate dyskinesia. The Foundation is working with several companies pursuing different approaches in this area including [mGluR5](#) (Addex Pharmaceuticals), [mu opioid receptors](#) (Adolor Corporation) and [nicotine](#) (Targacept, Inc.). The Foundation is also sponsoring a multi-site clinical trial targeting specific serotonin receptors that have been shown to play a role in dyskinesia. (For more information on top therapeutic targets, please see chart below.)

In addition to our focus on basal ganglia circuitry, we are driving several investigations focused on improving the delivery of levodopa, as this is believed to lead to dyskinesia in the first place.

Additionally, we are funding research to shed light on specific mechanisms underlying dyskinesia from a cell biology perspective.

Top Therapeutic Targets

mGluR5

- One promising approach to dyskinesia involves the glutamate receptor mGluR5. In five years the Foundation's de-risking efforts have chaperoned mGluR5 from basic discovery to clinical testing and attracted industry interest in the target. In August 2010, Addex Pharmaceuticals of Geneva received Foundation funding for a Phase 2 clinical trial of an mGluR5-targeting agent that has shown promise in pre-clinical trials and a Phase 1 clinical study. The Addex medicine, called ADX48621, is aimed at treating both aspects of dyskinesia, which comprises jerky movements known as chorea and slow, sometimes painful, writhing movements known as dystonia. The company's compound is the only experimental drug to have shown an impact on both aspects in pre-clinical testing.

The initial data on mGluR5 and dyskinesia came from a research group at Lund University in Sweden funded by the Foundation in 2005 to demonstrate that blocking the action of mGluR5 prevented levodopa-induced dyskinesias in rodent models of PD. Follow-on funding from MJFF allowed the researchers to collaborate with the University of Bordeaux in France, taking these to invest in mGluR5 development. Today, in addition to the Addex-funded trial, MJFF is supporting a team at The Institute for Neurodegenerative Disorders in New Haven, Connecticut, to verify the action of an mGluR5-targeting compound and determine a safe and effective dose for use in additional future clinical trials.

mu Opioid Receptors

- Scientific evidence suggests that increased opioid peptide transmission in the basal ganglia might underlie dyskinesia after chronic levodopa treatment and that opioid antagonists might be useful as adjuncts to levodopa therapy for Parkinson's disease. Preclinical evaluation of opioid antagonists in relevant models of dyskinesia suggests that antagonism of the mu opioid receptor may be effective for alleviating these levodopa-induced motor complications.

Exton, Pennsylvania-based biotech Adolor has discovered a family of novel, selective mu opioid receptors. These compounds have been shown to be highly efficacious, after oral administration, in well-validated pre-clinical models of dyskinesia. The robust antidyskinetic efficacy of these compounds was confirmed by three independent laboratories. Adolor's mu opioid receptors represent first-in-class compounds with a novel mechanism of action for the potential treatment of levodopa-induced dyskinesia associated with Parkinson's disease. MJFF is currently funding Adolor's ongoing lead compound optimization development efforts.

Serotonin

- Researchers at Lund University in Sweden have been funded by MJFF since 2005 to develop a new treatment for dyskinesia targeting the brain's serotonin system, better known for its role in clinical depression. With Foundation funding, the researchers recently demonstrated that abnormal, dyskinesia-inducing dopamine release can be effectively blocked by drugs that act on two specific receptors, known as 5-HT1A and 5-HT1B, located on the serotonin neurons. They have also shown that this technique is particularly effective when the two receptors are activated simultaneously.

Based on these results, Dr. Björklund's team is now conducting an MJFF-funded pilot clinical trial in 24 Parkinson's patients at Lund University Hospital and Karolinska Hospital Huddinge (both in Sweden). The trial is being carried out in collaboration with the U.S. biotech company PsychoGenics, using their proprietary drug Eltoprazine, which activates both 5-HT1A and 5-HT1B, and has shown promising results in pre-clinical trials to date.

Clinical Trial Infrastructure

Validation of Clinical Rating Scales for Dyskinesia

- The Michael J. Fox Foundation is funding a \$1-million clinical study aiming to establish a framework for testing novel anti-dyskinesia treatments by validating clinical scales used to measure changes in dyskinesia severity.

Significant problems in measuring dyskinesia and assessing the efficacy of potential new therapies have created major roadblocks to clear-cut trial results and, therefore, industry investment leading to new and better interventions. The establishment of validated tools for use in dyskinesia clinical trials would significantly reduce the barrier for biotech and pharmaceutical companies to invest in trials to address this debilitating aspect of living with Parkinson's.

The study holds two primary aims: quantitatively establish the degree of changes in dyskinesia severity as a result of treatment with amantadine; and conclusively determine which scale or scales most accurately detect these changes. Patients will be treated with amantadine or placebo, and then have their dyskinesia rated over the course of several weeks using numerous dyskinesia measurement scales. The researchers will examine the response to placebo as well in order to favor scales that maximally separate placebo-associated changes from amantadine-associated changes. The results will establish a path for clinical testing of future promising novel dyskinesia treatments.

The double-blind, placebo-controlled trial, enrolling 66 PD patients at up to eight sites in the United States, Canada and Europe, will be led by coordinating principal investigators Christopher G. Goetz, MD, and Glenn T. Stebbins, PhD, of Rush University Medical Center in Chicago.