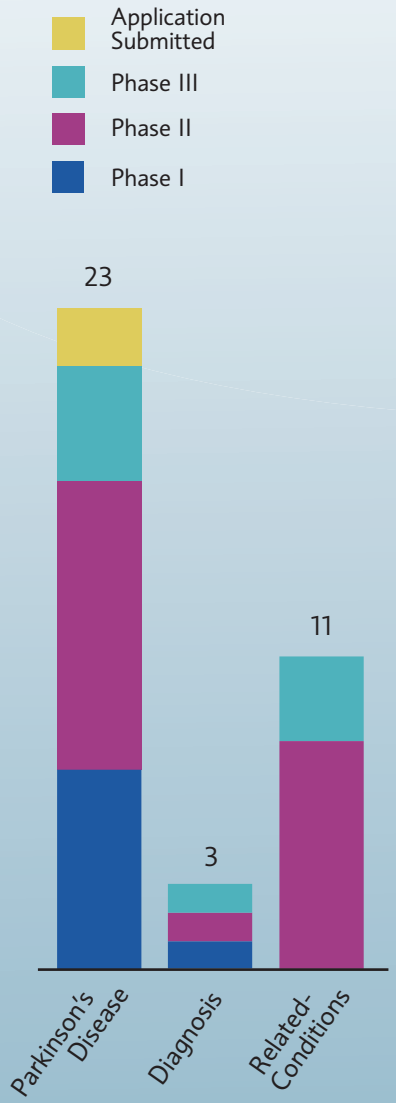
MEDICINES IN DEVELOPMENT

Parkinson's Disease

PRESENTED BY AMERICA'S BIOPHARMACEUTICAL RESEARCH COMPANIES

2014 REPORT

Medicines in Development For Parkinson's Disease



Nearly 40 Medicines Are Being Developed to Treat or Diagnose Parkinson's Disease and Related Conditions

Parkinson's disease affects as many as 1.5 million people in the United States, with about 60,000 additional patients newly diagnosed each year. The cost to the U.S. economy in direct and indirect expenses is more than $14 billion a year, according to a recent study published in *Movement Disorders*.

America's biopharmaceutical research companies are currently **developing 37 new medicines** to help patients suffering from Parkinson's disease, a chronic, progressive neurological disease. Considered a motor system disorder—resulting from the loss of dopamine-producing brain cells—symptoms include tremor, rigidity and instability and non-motor symptoms such as cognitive changes, difficulty swallowing and speaking, and sleep disruptions, among others.

All of the potential medicines are either in clinical trials or awaiting review by the U.S. Food and Drug Administration (FDA).

Research into new, effective treatments for Parkinson's disease has proven to be difficult, most likely because what actually causes the dopamine-producing cells to die off is not known. While most cases of Parkinson's disease happen spontaneously, some are believed to be hereditary. The exciting news is that recent advances and discoveries in science, including the identification of genes specific to Parkinson's, have sparked research and development into new treatment approaches.

The medicines in the R&D pipeline today offer hope of reducing the human and economic costs of Parkinson's disease. Some of these potential advances include:

- A gene therapy that targets the part of the brain that controls movement.
- A new medicine that targets a receptor found in the brain where degeneration and abnormality are often seen in Parkinson's disease.
- New delivery mechanisms of approved treatments, including an intranasal formulation and an intestinal gel.

Contents

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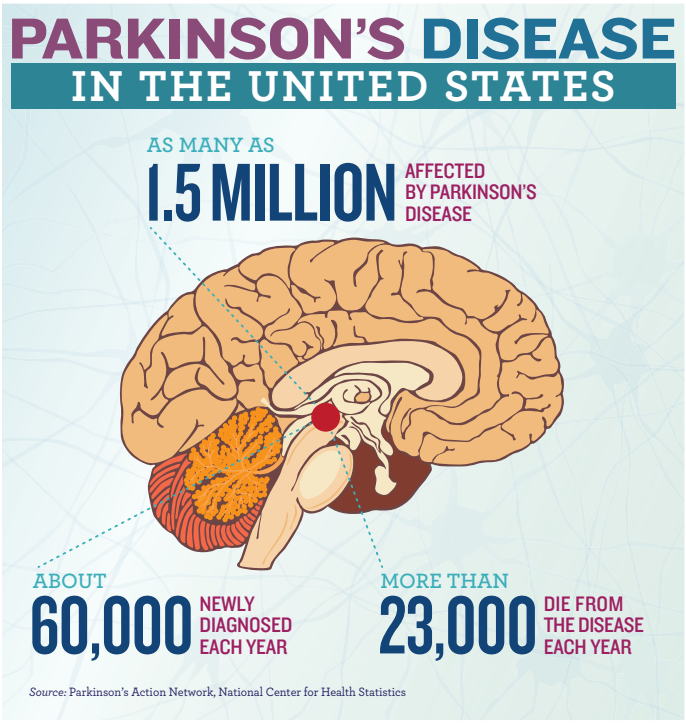
In addition, there are 43 active clinical trials in the United States for Parkinson's disease.[1] Of these trials, 30 have not yet started recruiting patients or are just now seeking volunteers to participate, and 13 are active but not recruiting new patients. These trials play a critical role in the development and testing of new treatments and represent potentially valuable therapeutic options for patients battling Parkinson's disease.

Researching and developing new medicines is an expensive and lengthy process. But advances in our understanding of diseases and how to treat them have allowed America's biopharmaceutical research companies to conduct the cutting-edge research needed to reduce the destructive toll of Parkinson's disease and allow more patients to lead healthier, fuller lives.



Approved Medicines for Parkinson's Disease

Research into Parkinson's disease has been difficult. According to experts, several barriers to developing therapies for Parkinson's exist, including a lack of a clear understanding about the biological processes leading to cell death in Parkinson's, inadequate translational research, and a lack of a biomarker for determining disease progression and severity.

In the last decade, five new medicines were approved to treat the motor and non-motor symptoms associated with Parkinson's disease. These new medicines are important for disease management and improved quality of life for patients. Earlier this year, **Northera™** (droxidopa) was approved to treat orthostatic hypotension, a debilitating drop in blood pressure when standing associated with Parkinson's disease.

In 2011, **DaTscan™** (Ioflupane I 123 injection) was approved as the first diagnostic imaging agent for evaluation of neurodegenerative movement disorders, specifically for helping differentiate between Parkinsonian syndromes and essential tremor. DaTscan is a radiopharmaceutical imaging agent that works by binding to dopamine transporters (DaT) in the brain. Use of DaTscan during single photon emission computed tomography (SPECT) brain imaging produces images that allows visualization of the presence of dopamine transporters.

[1] Source: *www.clinicaltrials.gov*. Criteria: United States, Phase 0, 1, 2 3; industry only.

Parkinson's Medicines in the Pipeline

Current medicines for Parkinson's disease are approved to treat the symptoms of the disease, such as mobility problems and tremors, but do not replace lost nerve cells or halt the progression of the disease itself. The loss of dopamine-producing cells in the brain is an underlying issue in Parkinson's disease. Several medicines in development are disease-modifying therapies focused on protecting brain cells in an attempt to halt disease progression, or treatments aimed at generating new cells or repairing damaged nerve cells.

- A **gene therapy** in development comprises an adeno-associated virus (AAV) vector that delivers the gene for aromatic L-amino acid decarboxylase (AADC) to cells in a part of the brain that controls movement. AADC is an enzyme that converts levodopa, a drug currently used to treat Parkinson's disease symptoms, to dopamine. As Parkinson's disease progresses, however, AADC activity declines and levodopa becomes less effective. Delivering AADC to the brain could restore the therapeutic effectiveness of levodopa and improve dopamine production.
- A potential **first-in-class medicine** targets a receptor found in the basal ganglia of the brain, where degeneration and abnormality are often seen in Parkinson's disease. Because

the basal ganglia play an important role in motor control, this medicine's distinct action makes it a potentially viable treatment for movement control challenges in later stages of the disease.

- An intraduodenal **gel formation** in development is a combination of levodopa (a version of dopamine that is able to travel from the blood to the brain by penetrating the blood brain barrier) and carbidopa, which helps prevent levodopa from being degraded before it reaches the brain. The medicine is delivered to the patient directly into the duodenum (first section of the small intestine) through a portable fusion pump. This mechanism of delivery helps prevent levodopa degradation and promotes faster absorption, and maintenance of more constant levels of levodopa. In standard levodopa therapy, the amount of levodopa in the blood can vary significantly, leading to inadequate maintenance of Parkinson's disease symptoms.

- A molecular imaging agent in development uses SPECT (single photon emission computed tomography) to aid in the **diagnosis of Parkinson's disease**. The imaging agent binds to the dopamine transporter (DAT) protein found on the surface of dopamine-producing neurons and is designed to measure the number of DATs in the region of the brain responsible for movement. Parkinson's patients have a reduced number of dopamine-producing neurons and a significantly lower number of DATs.

- A potential first-in-class treatment is being developed to treat Parkinson's disease psychosis (PDP). The medicine blocks the activity of a receptor that plays an important role in psychosis without blocking the therapeutic properties of dopamine. There are no approved treatments for PDP in the United States.

Early Research Shows Hope for New Treatments and Possible Cure

Although the actual cause or causes of Parkinson's disease is unknown, scientists have discovered that in individuals with Parkinson's, cells in the area of the brain called the "substantia nigra" die. These cells manufacture dopamine, a chemical that helps control muscle movement. Drug therapies have tended to focus on replacing dopamine or addressing specific symptoms associated with the disease.

Thanks to recent scientific advances, including the identification of several genes associated with Parkinson's, scientists can now research newly discovered pathways involved in the disease and uncover new targets for therapy. Some key breakthroughs include:

- Scientists at the National Institutes of Health (NIH) have discovered several genes that may provide new therapeutic targets for Parkinson's. Scientists believe these

genes regulate pathways involved in removing damaged or dysfunctional mitochondria, the power producers of the body's cells. Such pathways have been found to be disrupted or dysfunctional in some individuals with Parkinson's.

- Researchers at universities in the United Kingdom found that defects in a specific Parkinson's gene disrupt the body's ability to eliminate faulty mitochondria (a process called mitophagy). The researchers believe that drugs targeting mitophagy may lead to effective Parkinson's treatments.
- Scientists at the University of Bedfordshire have discovered how various elements in a single brain cell are responsible for how disease develops, providing insight that could lead to a cure for Parkinson's. The next step is finding how to protect cells from death.
- Researchers at Beth Israel Deaconess Medical Center have discovered that levels of the protein alpha-synuclein in skin tissue differ between Parkinson's patients and people without Parkinson's. This finding could lead to a biomarker for determining the risk of getting Parkinson's disease.

DETECTING PARKINSON'S DISEASE

Early diagnosis of Parkinson's disease will be important as new treatments are developed to stop or reverse the disease. It is estimated that Parkinson's patients lose up to 80 percent of dopamine-producing cells in their brains before symptoms of the disease appear. Results from special imaging tests of the brain suggest that dopamine may decline as much as 10 percent per year in people with Parkinson's. Early diagnosis and treatment are important to help minimize dopamine loss in the brain and maintain motor function. Currently, health care providers diagnose patients based on symptoms and whether those symptoms improve once treatment begins. One imaging agent has been approved to measure levels of dopamine in the brain to help confirm a diagnosis of Parkinson's.

Facts About Parkinson's Disease in the United States

Overview

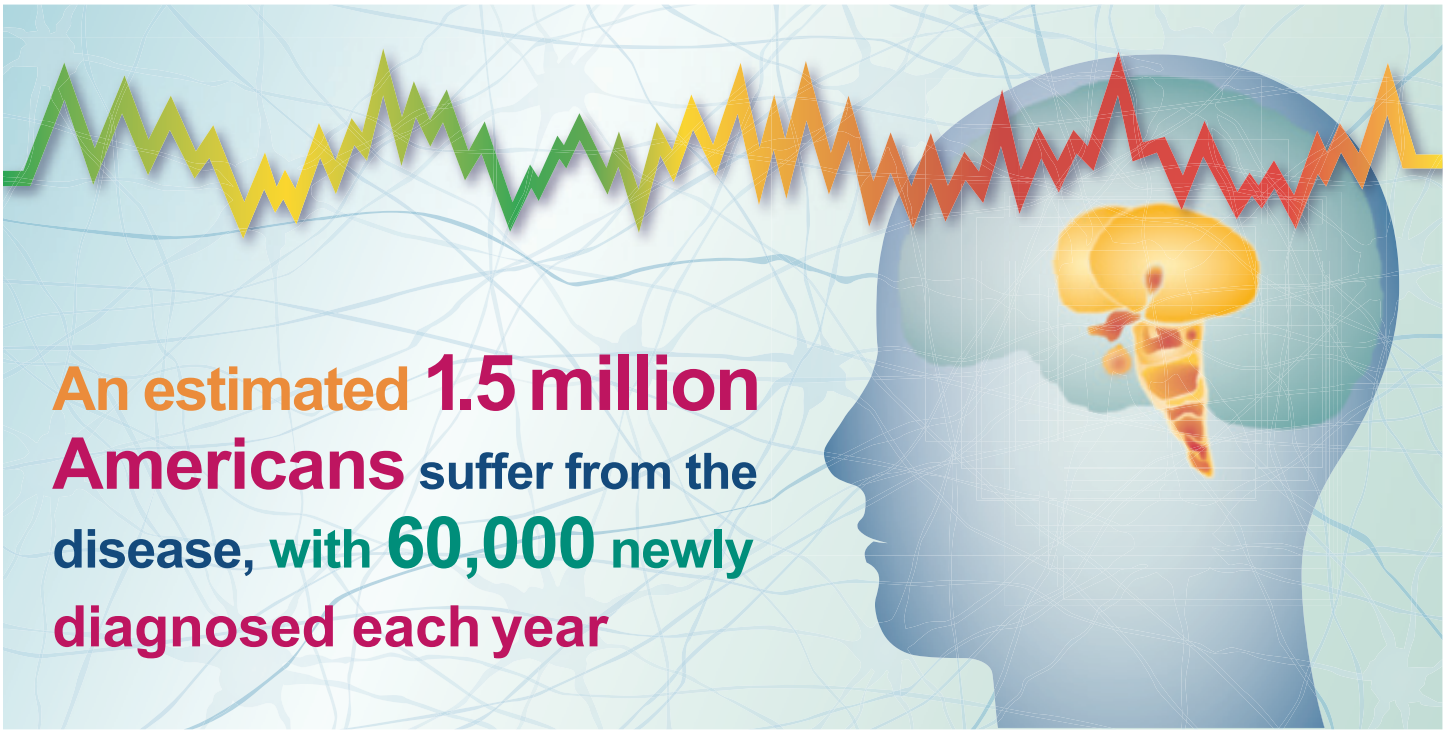
- The number of people in the United States with Parkinson's disease is estimated to be as many as 1.5 million. Approximately 60,000 Americans are newly diagnosed each year.[1]
- Parkinson's disease affects about 50 percent more men than women. The average age of onset of the disease is 60, with incidence increasing significantly with age. About 5 percent to 10 percent of people have "early-onset" disease that begins as early as age 50 or even earlier.[2]
- Some early-onset diagnoses are linked to specific gene mutations. Total risk for the disease is between 2 percent and 5 percent if no family members have a known gene mutation. About 15 percent to 25 percent of people with Parkinson's have a relative with the disease.[2]
- Parkinson's disease is the 14th leading cause of death in the United States.[3]

Economic Impact

- The economic burden of Parkinson's disease is at least $14.4 billion a year in the United States, with $8.1 billion in medical expenses and $6.3 billion in indirect costs attributed to the disease.[4]
- Medication treatment costs on average about $2,500 per patient. Therapeutic surgery could cost up to $100,000 per patient.[1]

Sources:

1. Parkinson's Action Network (*www.parkinsonsaction.org*)
2. National Institute of Neurological Disorders and Stroke (*www.ninds.nih.gov*)
3. National Center for Health Statistics, Centers for Disease Control and Prevention (*www.cdc.gov/nchs*)
4. "The Current and Projected Economic Burden of Parkinson's Disease in the United States," *Movement Disorders*, March 2013



Parkinson's Disease

Product Name	Sponsor	Indication	Development Phase*
AAV-hAADC gene therapy	Genzyme *Cambridge, MA* University of California San Francisco *San Francisco, CA* Voyager Therapeutics *Cambridge, MA*	Parkinson's disease	Phase I www.voyagertherapeutics.com
AAV2 GDNF gene therapy	UniQure *Amsterdam, Netherlands* University of California San Francisco *San Francisco, CA*	Parkinson's disease	Phase I www.uniqure.com
Ampyra® dalfampridine	Acorda Therapeutics *Ardsley, NY* University of Miami *Miami, FL*	Parkinson's disease (improve gait)	Phase I/II www.acorda.com
AVE8112 (PDE4 inhibitor)	The Michael J. Fox Foundation for Parkinson's Research *New York, NY* Sanofi US *Bridgewater, NJ*	Parkinson's disease	Phase I www.michaeljfox.org
AZD3241 (myeloper-oxidase [MPO] inhibitor)	AstraZeneca *Wilmington, DE*	Parkinson's disease	Phase II www.astrazeneca.com
BIA 9-1067 (opicapone)	Bial *Coronado, Portugal*	Parkinson's disease	Phase I completed www.bial.com
DopaFuse™ levodopa continuous infusion therapy	SynAgile *Piedmont, CA*	Parkinson's disease	Phase I www.synagile.com
Duodopa® levodopa/carbidopa intestinal gel ORPHAN DRUG	AbbVie *North Chicago, IL*	advanced Parkinson's disease (Fast Track)	application submitted www.abbvie.com
GM608	Genervon Biopharmaceuticals *Pasadena, CA*	Parkinson's disease	Phase II www.genervon.com
HT-1067 (MOA-B inhibitor)	Dart NeuroScience *San Diego, CA*	Parkinson's disease	Phase I www.dartneuroscience.com

*For more information about a specific medicine or company in the report, please use the website provided.

Parkinson's Disease

Product Name	Sponsor	Indication	Development Phase
IPX203	Impax Pharmaceuticals *Hayward, CA*	Parkinson's disease	Phase II www.impaxpharma.com
istradefylline (KW-6002)	Kyowa Hakko Kirin Pharma *Princeton, NJ*	severe Parkinson's disease	Phase III www.kyowa-kirin-pharma.com
levodopa inhalation (CVT-301)	Civitas Therapeutics *Chelsea, MA*	Parkinson's disease (adjunctive therapy)	Phase II www.civitastherapeutics.com
LY03003 (rotigotine extended-release microsphere formulation)	Luye America Pharmaceuticals *Princeton, NJ*	Parkinson's disease (early-stage disease)	Phase I www.luye.cn/en/
OS-320 (levodopa/carbidopa)	Osmotica Pharmaceutical *Wilmington, NC*	Parkinson's disease	Phase III www.osmotica.com
P2B001 (pramipexole/rasagiline fixed-dose combination)	Pharma Two B *Rehovot, Israel*	Parkinson's disease (early-stage disease)	Phase II www.pharma2b.com
Phosphen® R-phenserine	QR Pharma *Berwyn, PA*	Parkinson's Disease	Phase II www.qrpharma.com
Rytary™ levodopa/carbidopa extended release	Impax Pharmaceuticals *Hayward, CA*	idiopathic Parkinson's disease	application submitted www.impaxpharma.com
safinamide	Newron Pharmaceuticals *Bresso, Italy*	early-stage Parkinson's disease (adjunctive therapy) --- late-stage and mid-stage Parkinson's disease (adjunctive therapy)	Phase III www.newron.com --- Phase III www.newron.com
tozadenant (SYN-115)	Biotie Therapies *South San Francisco, CA* UCB *Brussels, Belgium*	Parkinson's disease (adjunctive therapy)	Phase II/III www.biotie.com www.ucb.com
V81444	Vernalis *Winnersh, United Kingdom*	Parkinson's disease	Phase I/II www.vernalis.com
vatiquinone	Edison Pharmaceuticals *Mountain View, CA*	Parkinson's disease	Phase II www.edisonpharma.com

Parkinson's Disease

Product Name	Sponsor	Indication	Development Phase
XP21279	XenoPort *Santa Clara, CA*	Parkinson's disease	Phase II www.xenoport.com

Parkinson's Disease—Diagnosis

Product Name	Sponsor	Indication	Development Phase
florbenazine (18F-AV-133)	Eli Lilly *Indianapolis, IN*	Parkinson's disease (diagnosis)	Phase II www.lilly.com
NAV5001 (123-I labeled imaging agent)	Navidea Biopharmaceuticals *Dublin, OH*	Parkinsonian disorders (diagnosis)	Phase III www.navidea.com
NuroPro® neurotrophic factor companion diagnostic	Amarantus BioScience *San Francisco, CA*	Parkinson's disease (diagnosis)	Phase I www.amarantus.com

Parkinson's Disease—Related Conditions

Product Name	Sponsor	Indication	Development Phase
ADS-5102 (amantadine controlled release)	Adamas Pharmaceuticals *Emeryville, CA*	levodopa-induced dyskinesia	Phase II/III www.adamaspharma.com
AQW051 (alpha7 nicotinic receptor)	Novartis Pharmaceuticals *East Hanover, NJ*	levodopa-induced dyskinesia	Phase II completed www.novartis.com
AVP-923 (dextromethorphan/quinidine)	Avanir Pharmaceuticals *Aliso Viejo, CA*	levodopa-induced dyskinesia	Phase II www.avanir.com
camicinal (motilin receptor agonist)	GlaxoSmithKline *Research Triangle Park, NC*	gastroparesis in Parkinson's disease	Phase II www.gsk.com
dipraglurant-IR (ADX48621)	Addex Therapeutics *Geneva, Switzerland*	levodopa-induced dyskinesia	Phase II www.addextherapeutics.com
eltoprazine	Amarantus BioScience *San Francisco, CA*	levodopa-induced dyskinesia	Phase II www.amarantus.com

Parkinson's Disease—Related Conditions

Product Name	Sponsor	Indication	Development Phase
Myobloc® rimabotulinumtoxinB	US WorldMeds *Louisville, KY*	sialorrhea associated with Parkinson's disease	Phase III www.usworldmeds.com
NH004 (tropicamide buccal film)	NeuroHealing Pharmaceuticals *Waban, MA*	sialorrhea associated with Parkinson's disease	Phase II www.neurohealing.com
pimavanserin (ACP-103)	ACADIA Pharmaceuticals *San Diego, CA*	Parkinson's disease psychosis	Phase III www.acadia-pharm.com
RM-131 (ghrelin agonist)	Rhythm Pharmaceuticals *Boston, MA*	constipation in Parkinson's disease	Phase II www.rhythmtx.com
Xeomin® incobotulinumtoxinA	Beth Israel Deaconess Medical Center *Boston, MA* Merz *Frankfurt, Germany*	sialorrhea associated with Parkinson's disease	Phase II www.merz.com

The content of this report has been obtained through public, government and industry sources, and the Adis "R&D Insight" database based on the latest information. **Report current as of February 26, 2014.** *The medicines in this report include medicines being developed by U.S.-based companies conducting trials in the United States and abroad, PhRMA-member companies conducting trials in the United States and abroad, and foreign companies conducting clinical trials in the United States. The information in this report may not be comprehensive. For more specific information about a particular product, contact the individual company directly or go to* ***www.clinicaltrials.gov****. The entire series of Medicines in Development is available on PhRMA's website.*

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Glossary

adjunctive treatment—An auxiliary treatment that is secondary to the main treatment.

application submitted—An application for marketing has been submitted by the company to the U.S. Food and Drug Administration (FDA).

duodenum—the first section of the small intestine.

dyskinesia—An impairment in the ability to control movements, characterized by spasmodic or repetitive motions or lack of coordination. Although the drug levodopa effectively eliminates the major motor symptoms of Parkinson's disease, long-term use of levodopa can lead to development of dyskinesia, which can reduce the benefit of levodopa treatment over time.

Fast Track—A process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need. The status is assigned by the U.S. Food and Drug Administration (FDA). The purpose of this process is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious diseases. In general, determining factors for whether a drug receives Fast Track include whether the drug will affect factors such as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy that may be potentially superior to existing therapy. Once a drug receives Fast Track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication ensures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

gastroparesis—A condition where the movement of food from the stomach to the small intestine stops or slows down. It does not involve a blockage or obstruction. The muscles in the stomach break up food and move it through the gastrointestinal tract. In gastroparesis, the vagus nerve, which controls the stomach muscles, is damaged by illness or injury and the stomach muscles stop working.

gene therapy—Therapy at the intracellular level to replace or inactivate the effects of disease-causing genes or to augment normal gene functions to overcome illness.

idiopathic—Meaning the cause of a disease or condition is not known or happens spontaneously.

imaging agent—A substance used to enhance x-ray images of organs and spaces in the body.

levodopa—A treatment for Parkinson's disease used to increase the dopamine in a patient's brain. It is able to move from the blood into the brain through the protective blood-brain barrier, whereas dopamine cannot.

Orphan Drug—A drug to treat a disease that has a patient population of 200,000 or less in the United States, or a disease that has a patient population of more than 200,000 and a development cost that will not be recovered from sales in the United States.

orthostatic hypotention—A drop in blood pressure that occurs when changing position from lying to sitting or from sitting to standing, which causes lightheadedness or dizziness. It is a common symptom of Parkinson's disease and can make patients pass out or fall.

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 disease are tremor, or trembling in hands, arms, legs, jaw, or face; rigidity, or stiffness of the limbs and trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance and coordination. Parkinson's is both chronic, meaning it persists over a long period of time, and progressive, meaning its symptoms grow worse over time. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. Early symptoms of Parkinson's are subtle and occur gradually. In some people, the disease progresses more quickly than in others. As the disease progresses, the tremor, which affects the majority of Parkinson's patients, may begin to interfere with daily activities. Other symptoms may include depression and other emotional changes; difficulty in swallowing, chewing, and speaking; urinary problems or constipation; skin problems; and sleep disruptions. Some people become severely disabled. No one can predict which symptoms will affect an individual patient, and the intensity of the symptoms varies from person to person.

Phase 0—First-in-human trials conducted in accordance with FDA's 2006 guidance on exploratory Investigational

New Drug (IND) studies designed to speed development of promising drugs by establishing early whether the tested compound behaves in humans as was anticipated from preclinical studies.

Phase I—Researchers test the drug in a small group of people, usually between 20 and 80 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Phase II—The drug is given to volunteer patients, usually between 100 and 300, to determine whether the drug is effective, identify an optimal dose, and to evaluate further its short-term safety.

Phase III—The drug is given to a larger, more diverse patient population, often involving between 1,000 and 3,000 patients (but sometimes many more thousands), to generate statistically significant evidence to confirm its safety and effectiveness. Phase III studies are the longest studies and usually take place in multiple sites around the world.

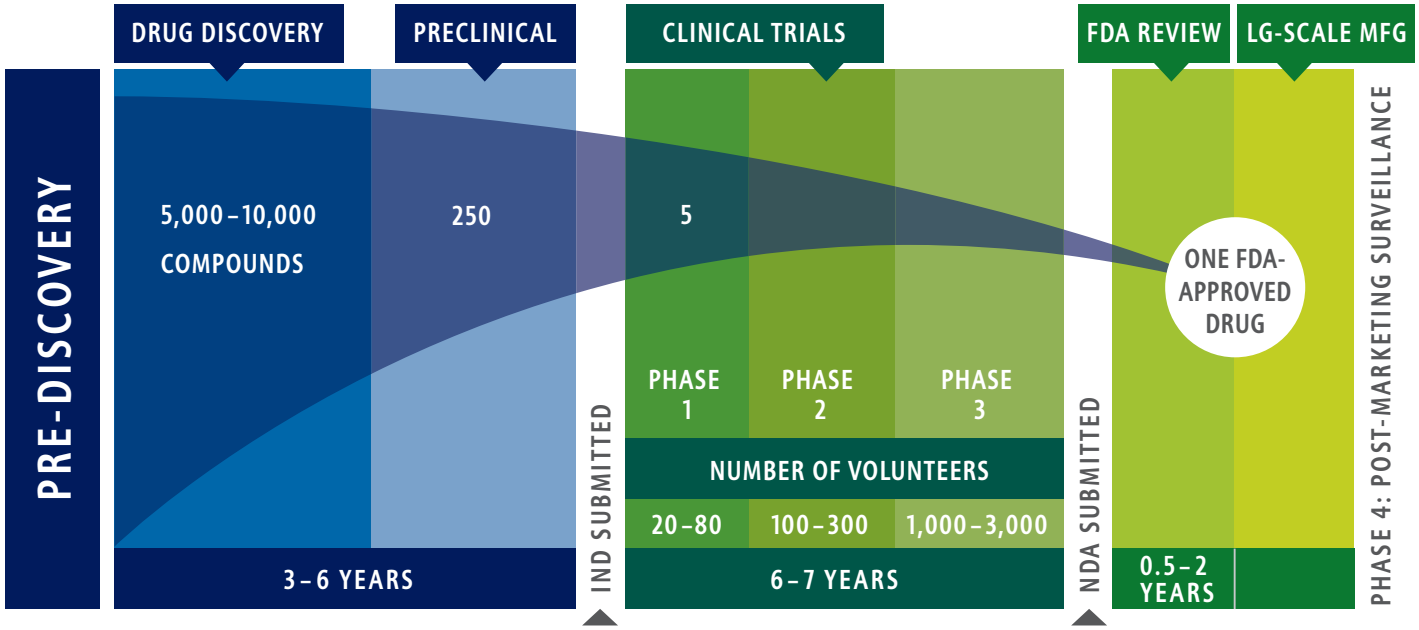
psychosis—Psychosis can occur in people with Parkinson's disease. It can affect as many as 1 in 5 patients with the disease. Symptoms include delusions, hallucinations, thought disorders, loss of emotion, mania, and depression.

sialorrhea—Drooling or excessive salivation, which is a common problem in neurologically impaired children (e.g., those with intellectual or developmental disabilities) and in adults who have Parkinson's disease or have had a stroke. It is commonly most caused by poor oral and facial muscle control.

The Drug Discovery, Development and Approval Process

Developing a new medicine takes an average of 10-15 years;
For every 5,000-10,000 compounds in the pipeline, only 1 is approved.

Drug Discovery and Development: A LONG, RISKY ROAD



The Drug Development and Approval Process

The U.S. system of new drug approvals is perhaps the most rigorous in the world.

It takes 10-15 years, on average, for an experimental drug to travel from lab to U.S. patients, according to the Tufts Center for the Study of Drug Development. Only five in 5,000 compounds that enter preclinical testing make it to human testing. And only one of those five is approved for sale.

On average, it costs a company $1.2 billion, including the cost of failures, to get one new medicine from the laboratory to U.S. patients, according to a recent study by the Tufts Center for the Study of Drug Development.

Once a new compound has been identified in the laboratory, medicines are usually developed as follows:

Preclinical Testing. A pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

Investigational New Drug Application (IND). After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration (FDA) to begin to test the drug in people. The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted. Progress reports on clinical trials must be submitted at least annually to FDA and the IRB.

Clinical Trials, Phase I—Researchers test the drug in a small group of people, usually between 20 and 80 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Clinical Trials, Phase II—The drug is given to volunteer patients, usually between 100 and 300, to see if it is effective, identify an optimal dose, and to further evaluate its short-term safety.

Clinical Trials, Phase III—The drug is given to a larger, more diverse patient population, often involving between 1,000 and 3,000 patients (but sometime many more thousands), to generate statistically significant evidence to confirm its safety and effectiveness. They are the longest studies, and usually take place in multiple sites around the world.

New Drug Application (NDA)/Biologic License Application (BLA). Following the completion of all three phases of clinical trials, a company analyzes all of the data and files an NDA or BLA with FDA if the data successfully demonstrate both safety and effectiveness. The applications contain all of the scientific information that the company has gathered. Applications typically run 100,000 pages or more.

Approval. Once FDA approves an NDA or BLA, the new medicine becomes available for physicians to prescribe. A company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional trials (Phase IV) to evaluate long-term effects.

Discovering and developing safe and effective new medicines is a long, difficult, and expensive process. PhRMA member companies invested an estimated $48.5 billion in research and development in 2012.