

MEDICINES IN DEVELOPMENT FOR NEUROLOGICAL DISORDERS

A REPORT ON DISORDERS OF THE BRAIN, SPINAL CORD AND NERVES

Biopharmaceutical Researchers are Developing More Than 400 Medicines for Wide Range of Neurological Disorders

Neurological disorders comprise more than 600 conditions that affect the nervous system. Together, these disorders impact an estimated 50 million Americans every year. Although some are well known, such as epilepsy, multiple sclerosis and Parkinson's disease, many are rare disorders affecting just a small number of patients.¹ According to a study from the Bill and Melinda Gates Foundation, neurological disorders represent eight percent of the global health burden, with stroke, migraine, and epilepsy being the top contributors.

In recent years, scientists have learned more about how the nervous system works at the molecular and genetic levels, helping to develop more effective treatments for neurological disorders. However, many disorders still do not have an approved treatment or are in need of newer, more effective treatments. Biopharmaceutical research companies are in the process of developing 420 medicines³ to prevent and treat a number of neurological disorders. The medicines in development are either in human clinical trials or under review at the Food and Drug Administration (FDA).

The medicines in development include:

94 medicines for chronic pain, which affects 100 million Americans.⁴

59 medicines for Alzheimer's disease, which affects more than 5 million Americans.⁵

58 for brain tumors, including gliomas, which represent 80 percent of all malignant tumors.⁶

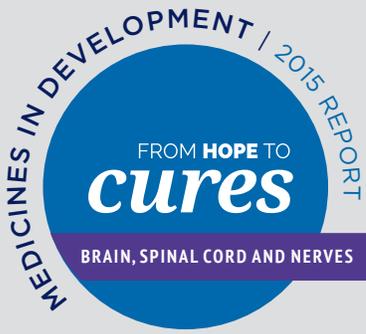
33 medicines for multiple sclerosis, which affects as many as 500,000 Americans.⁷

31 medicines for Parkinson's disease, which affects as many as 1 million Americans.⁸

22 medicines for epilepsy and seizures, which affect nearly 3 million Americans.⁹

Other medicines in development target amyotrophic lateral sclerosis (ALS), brain injuries, Huntington's disease, migraine, spinal cord injury, neurological genetic disorders, and stroke.

Some medicines are listed in more than one category. For a complete list of the 420 medicines in development, please visit http://phrma.org/sites/default/files/pdf/2015-neurological-disorders_drug-list.pdf



JUST THE FACTS

50 MILLION

Estimated number of Americans affected by neurological disorders¹

600

Approximate number of different neurological disorders¹

8%

Global health burden of neurological disorders²

420

Number of medicines in development for neurological disorders³

Medicines in Development FOR NEUROLOGICAL DISORDERS



in the neurons most damaged in Huntington's. Huntington's disease is an inherited disorder caused by the programmed degeneration of brain cells, called neurons, in certain areas of the brain. This degeneration can lead to uncontrolled movements, loss of intellectual faculties, and emotional disturbances. Inhibition of the PDE10A enzyme has been shown to improve cell function and potentially provide neuroprotective effects.

- A monoclonal antibody in development for amyotrophic lateral sclerosis (ALS) is an inhibitor of the protein Nogo-A. Research suggests that Nogo A may be involved in the pathology of ALS. Motor neurons signal the body's muscles to move. In ALS, the junctions that transmit signals from the motor neurons to the muscles begin to degenerate, leading to muscle weakness, paralysis, and respiratory failure. Inhibiting Nogo-A protein may help keep the motor neurons and muscle fibers connected in hopes that it will lead to a slowing or stopping of disease progression.
- A monoclonal antibody in development for relapsing multiple sclerosis targets LINGO, a protein that is involved in the development of myelin, a protective sheath covering the nerve fibers. In multiple sclerosis, the body's immune system attacks myelin. Damage to myelin disrupts communication among cells throughout the nervous system, impairing mobility, vision and thinking. Over time, the nerves can become permanently damaged. It is believed that LINGO may inhibit myelin growth and, by blocking LINGO's production, the medicine could support the growth of myelin and restore nerve communication in multiple sclerosis patients. This medicine is also being studied as a treatment for acute optic neuritis, an inflammation of the optic nerve that is associated with multiple sclerosis.

Medicines in Development for Neurological Disorders

The new medicines under development by biopharmaceutical research companies represent a growing understanding of the underlying mechanisms of neurological disorders. This enhanced understanding – fueled by both successes and setbacks in research – creates scientific progress over time. Many of the 420 medicines in the pipeline include treatments that explore new pathways and scientific approaches to treat these complex disorders. Examples of innovative treatments in development include:

- A monoclonal antibody in development for the prevention of migraine binds to and inhibits the activity of calcitonin gene-related peptide (CGRP). CGRP is expressed in the nervous system, where it plays a role in controlling the widening of blood vessels and the transmission of nociceptive pain (pain arising from nerve cells) information. Research suggests that CGRP pathways may be involved in the development of migraines. By inhibiting CGRP activity, anti-CGRP antibodies are thought to help inhibit the transmission of pain signals associated with migraines.
- About 300,000 American children under the age of 14 have epilepsy.

A medicine, already approved for use by adults, is in clinical trials for pediatric partial onset seizures. Seizures begin in the brain, which is made up of millions of nerve cells which communicate with each other by sending electrical signals. In people with epilepsy, overexcited nerve cells send too many electrical signals that can then cause seizures. The medicine works by reducing the number of "extra" electrical signals that are sent out. The medicine is also being studied in pediatric and adult populations for primary generalized tonic-clonic seizures.

- A medicine in development for Huntington's disease targets the PDE10A enzyme, which is present

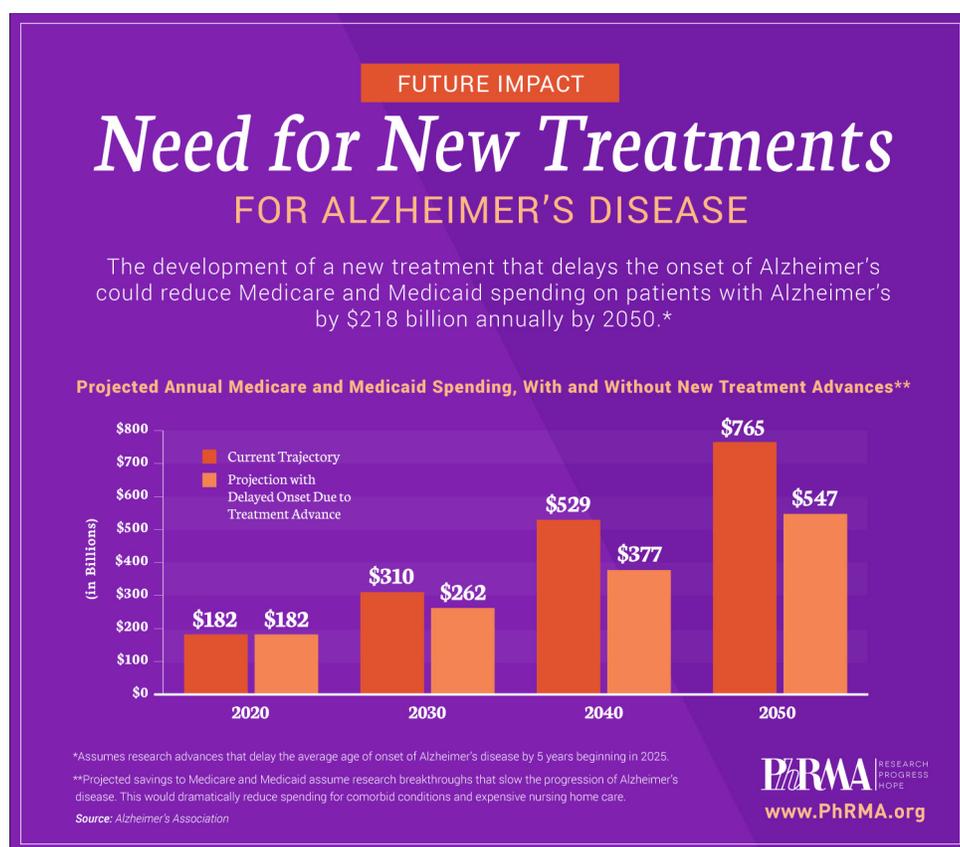
EPILEPSY IS THE FOURTH-MOST COMMON NEUROLOGICAL CONDITION IN THE UNITED STATES, WITH ABOUT 150,000 AMERICANS DEVELOPING SOME FORM OF THE DISORDER EACH YEAR.

The Need for New Treatments for Neurological Disorders

SPOTLIGHT: ALZHEIMER'S DISEASE

Alzheimer's is the sixth-leading cause of death in the United States, and its impact on patients and the health care system is growing. Existing medicines treat the symptoms of the disease but cannot slow, prevent or reverse the progressive deterioration and dementia it causes. The development of disease-modifying treatments that delay the onset of Alzheimer's could reduce Medicare and Medicaid spending on

patients with Alzheimer's by more than \$218 billion annually by the year 2050.¹⁰ Researchers continue to unravel the mysteries of the disease and are studying many new treatments in this area. Recent research has focused on the plaques and tangles that form in the brains of Alzheimer's patients and are thought to contribute to the death of nerve cells.



SPOTLIGHT: EPILEPSY

Epilepsy is a chronic disorder characterized by recurrent seizures. People who suffer from the disorder often experience more than one type of seizure and may have other neurological conditions as well. Epilepsy is the fourth-most common neurological condition in the United States, with about 150,000 Americans

developing some form of the disorder each year.

Seizures occur in the human brain but the causes vary and are often unknown. A seizure is a disruption of the electrical communication between neurons, and – although the symptoms of a seizure can affect any part of the body – the electrical events that produce the

symptoms stem from the brain. Epilepsy can significantly affect a person's day-to-day life impacting relationships, work and safety.

While there are effective treatments available for epilepsy patients, about

one-third live with uncontrolled seizures. And many more live with less-than-optimal seizure control and/or experience undesirable side effects from their treatment.

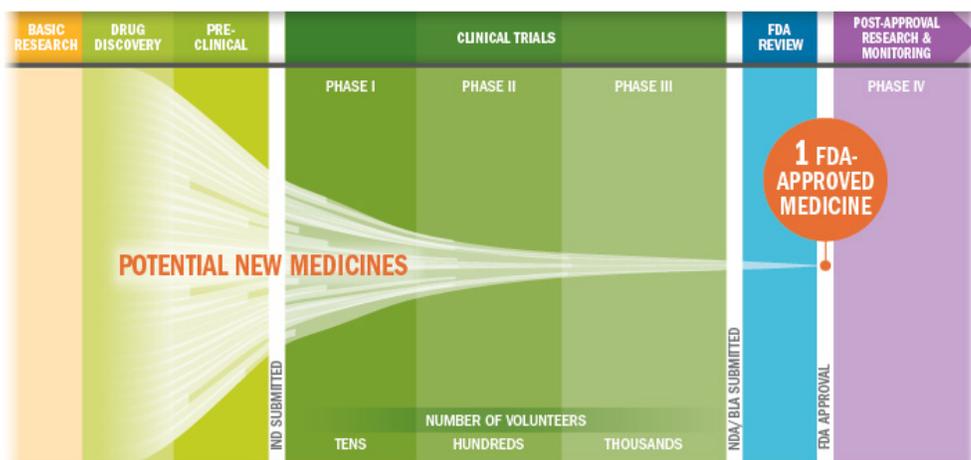
SPOTLIGHT: HUNTINGTON'S DISEASE

Huntington's disease (HD) is an inherited disorder that causes a progressive breakdown of nerve cells in the brain. Although patients with HD are born with the defective gene associated with HD, symptoms generally do not appear until middle age—typically between the ages of 30 and 50. However, the onset of HD can occur as young as the age of two. It is estimated that 30,000 Americans have the disease and another 200,000 are at-risk of inheriting the disease.¹¹ HD has a significant effect on a person's functional abilities and usually results in movement, cognitive, and mental health disorders. Children developing HD rarely live to adulthood. Weakened HD patients generally succumb to pneumonia, heart failure, or other complications.

Although there is no cure for HD, recently approved treatments are helping patients manage symptoms and improve their quality of life. The first treatment for HD, tetrabenazine, was approved by the FDA in 2008 and reduces involuntary movements (chorea) by modifying chemical pathways in the brain. Lessening the burden of chorea for HD patients helps improve their overall quality of life and allows them to take part in normal daily activities.

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of \$2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Sources: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf> (accessed Jan. 20, 2015).

Footnotes:

1. National Institute of Neurological Disorders and Stroke.
2. Bill and Melinda Gates Foundation.
3. Number of medicines obtained through public, government and industry sources, and the Adis "R&D Insight" database; current as of May 11, 2015.
4. The American Academy of Pain Medicine.
5. Alzheimer's Association.
6. American Brain Tumor Association.
7. Multiple Sclerosis Foundation.
8. National Parkinson Foundation.
9. Epilepsy Foundation.
10. Institute of Medicine of the National Academies.
11. Huntington's Disease Society of America.

