

Executive Summary

Neurodegenerative diseases are conditions caused by the loss or dysfunction of neurons in the brain or spinal cord. These diseases are especially devastating because they affect cells that cannot typically regenerate or replace themselves following damage or death. This report deals with chronic neurodegenerative diseases by focusing on four of the most comprehensively studied such conditions: Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS).

These four diseases have many common features. They are usually caused by a combination of genetic and environmental influences, though virtually all cases of HD and a small percentage of cases of the other three disorders are purely familial. They are associated with aging and are progressive and irreversible, causing gradually increasing disability over the course of years until they ultimately result in death. The neuronal damage they inflict produces imbalances in the system of neurotransmitters, the chemical messengers that are involved at the cellular level in modulating brain functions like movement and memory. They were first described over a century ago, but much work remains to be done to fully understand their disease processes. They have complex pathologies, characterized by the involvement of a multiplicity of molecular pathways, including oxidative stress, glutamate excitotoxicity, mitochondrial dysfunction, and abnormal protein aggregation.

To the pharmaceutical industry, perhaps the most important defining characteristic of these four diseases is the inadequacy of the standard of care. While treatments exist, they tend in most cases to only address symptoms as opposed to modifying disease course. Several relatively new drugs are available for AD, but they have only modest effects that pale in the face of the steady deterioration that marks the disorder. There is a larger formulary on hand for PD, including several classes of compounds for treating motor symptoms, but these are weakened by the issues of side effects and diminishing returns. The landscape is even bleaker for HD and ALS, with only a single, moderately effective drug for each of these conditions after decades of research.

As a result, neurodegenerative diseases are drawing immense interest from the pharmaceutical industry and have inspired heavy competition in the race to introduce the next generation of improved drugs. AD and PD, in particular, present huge potential markets, with five million and one million patients, respectively, in the United States alone. HD and ALS are quite uncommon in comparison, with only about 30,000 US patients apiece, but all four diseases disproportionately affect the elderly, who comprise a steadily increasing share of the population in the developed world. All four are chronic, progressive conditions, and with the exception of an outright cure, most symptomatic or disease-modifying therapies would most likely require regular administration over the course of years to keep the disease at bay. Thus, a confluence of factors—large and growing markets, the need for long-term treatment, and therapeutic voids to be filled—suggests that a company that can deliver an improved compound for one of these neurodegenerative disorders will earn a rich return on its investment.

Developing effective drugs for these diseases has been and continues to be a challenging prospect, though. AD, PD, HD, and ALS are pathologies that attack the most complex and least understood region of human anatomy: the nervous system. Researchers have figured out different aspects of the mechanisms of the diseases, but are unsure how the various pieces fit together into pathogenic pathways. As a result, drug development has been a slow and painstaking process, with many incremental advancements and more than a few reversals. AD research, for example, has been stung by the recent setbacks of several novel compounds in Phase III trials. PD is an active field, but the greatest progress has been with next-generation versions of drugs that are already available. And in HD and ALS, the late-stage clinical candidates are most often nonspecific drugs that were originally developed for other indications altogether. As a general trend, the novel, disease-targeted compounds tend to be further back in the pipeline than the “copycats” and “generalists.” This may mean that true breakthrough drugs are still several years away, at a minimum.

This report offers an in-depth analysis of these four neurodegenerative diseases, beginning in Chapter 1 with a review of their symptoms and pathology, their presumed causes, their methods of diagnosis, and their epidemiology. Chapter 2 discusses the existing drug therapies for each of the disorders. Chapter 3, forming the bulk of the report, is dedicated to surveys of the R&D picture for each of the diseases, including tables of the approximately 150 compounds in clinical development and discussions of particularly noteworthy drug candidates. Chapter 4 summarizes with conclusions and an outlook on the need to find better treatments for these diseases.