CAS INSIGHTS™
NEURODEGENERATIVE DISORDERS
Deciphering Nervous System Decline
Neurodegenerative diseases represent a spectrum of disorders that are characterized by the progressive destruction of cells and connections that make up the nervous system. These conditions are detrimental to the lives of millions of people worldwide, ultimately leading to the collapse of the neural networks that are required for human function.\(^1\)

Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis, and polyglutamine (polyQ) diseases all belong to the neurodegenerative classification, and we will delve deeper into specific conditions throughout this report.\(^2\)–\(^5\)

In people with neurodegenerative disorders such as those aforementioned, cells of the nervous system, called neurons, are progressively damaged and destroyed, resulting in the breakdown of the core communicative connections.\(^1\) Depending on the specific disease, this degeneration can lead to impaired memory, cognition, behavior, sensory, and/or motoric performance.\(^1\) Neurodegenerative diseases remain incurable, but certain disorders can be treated to provide symptomatic relief, improve quality of life, or limit disease progression.

Older age has been associated with an increased risk of developing a neurodegenerative condition, and the rise in longevity over the past decades has coincided with an increased incidence of neurodegenerative disorders. With an increasing aging population worldwide, effective treatment and management of these conditions becomes paramount.\(^6\)

It has been proposed that neurodegenerative diseases are defined by a set of common attributes, including pathological protein aggregation, synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy metabolism, DNA and RNA defects, inflammation, and neuronal cell death (\textbf{Figure 1}).\(^1,6\)–\(^8\)

In this report, we examine data from the CAS Content Collection\textsuperscript{TM}, the largest human-compiled multi-disciplinary database of published documents and substances, to inform readers about the latest advances in the management of neurodegenerative disorders.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Hallmarks of neurodegenerative diseases and relationships between them.\(^1,6\)–\(^8\)}
\end{figure}
Neurodegeneration: The global impact

Figure 2 depicts the worldwide prevalence of several notable neurodegenerative diseases, along with the number of documents related to these diseases in the CAS Content Collection. Neurodegenerative disorders not only harm the lives of individuals with the condition, but can also be distressing for their loved ones.

Figure 2. Worldwide prevalence of major neurodegenerative diseases (outer circle) and distribution of the number of documents related to those diseases in the CAS Content Collection (inner circle). ALS, amyotrophic lateral sclerosis; FD, frontotemporal dementia; LBD, Lewy body dementia; MS, multiple sclerosis; PD, Parkinson’s disease; polyQ, polyglutamine.
AD: The leading cause of dementia

Data from the World Health Organization suggests that approximately 50 million people live with dementia worldwide, and AD accounts for 60–70% of cases. The prevalence of AD increases with age, and the majority of cases occur in individuals over 65 years old. As life expectancy increases globally, the number of people living with AD is expected to rise substantially in the coming decades.\textsuperscript{10,11}

AD is associated with abnormal deposits of specific proteins in the brain, specifically beta-amyloid plaques and tau tangles.\textsuperscript{12} These deposits disrupt communication between brain cells and lead to their eventual death, resulting in widespread neuronal loss in brain regions critical for memory and cognitive function, such as the hippocampus and cerebral cortex (Figure 3).\textsuperscript{12}

Individuals with AD experience a progressive decline in cognitive function, memory loss, and changes in behavior and personality, leading to a loss of independence and ability to perform daily tasks. As the disease progresses, individuals become increasingly dependent on others for assistance with activities of daily living. In the advanced stages of AD, individuals may lose the ability to communicate verbally, recognize loved ones, or control movement. This means that people with AD often require round-the-clock care in a residential facility or at home with the assistance of caregivers. Physical complications such as infections, falls, and malnutrition become more common with advanced disease, contributing to further decline in health.

Unsurprisingly, AD has a profound impact on individuals, families, and society as a whole. The economic impact of AD is substantial, including direct medical costs for diagnosis, treatment, and long-term care, as well as indirect costs associated with lost productivity and caregiver burden.

Figure 3. Pathological hallmarks of AD.
**PD: The movement disorder**

PD is the second most common neurodegenerative disorder after AD. Its prevalence increases with age, with the majority of cases occurring in individuals over the age of 60. Estimates of prevalence vary globally, but it is generally reported to affect around 1–2% of individuals over the age of 65. Prevalence rates tend to be higher in industrialized regions, such as Europe and North America, compared to developing nations.

PD primarily affects movement and is caused by the gradual loss of dopamine-producing neurons in a section of the brain called the substantia nigra. Dopamine is a ‘neurotransmitter’ and is involved in coordinating movement. Dopamine deficiency leads to the characteristic motor symptoms of PD, including tremors, bradykinesia (slowness of movement), muscle rigidity, and postural instability. The effects of PD are not necessarily restricted to impaired motor functions, and the condition can cause cognitive decline, depression, and sleep disturbances.

While the exact cause of PD is not fully understood, it is believed to involve a combination of genetic, environmental, and age-related factors.

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**Figure 4. Pathological hallmarks of PD.**

- **Healthy brain pathway**
  - Dopamine
  - Substantia nigra

- **Parkinson’s disease**
  - Aggregation of α-synuclein proteins
  - Lewy body
  - Impairment and loss of melanated dopaminergic neurons
  - Accumulation of Lewy bodies

- **Affected dopamine pathways**
  - **Nigrostriatal**
    - Voluntary movement production
  - **Mesocortical**
    - Cognition
    - Memory and learning
    - Motivation
  - **Mesolimbic**
    - Emotion
    - Perception
    - Reward
  - **Tubero-infundibular**
    - Sensory processing
    - Hormonal regulation
    - Maternal nurturing

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**Figure 4. Pathological hallmarks of PD.**
PolyQ diseases: Rare conditions with a big impact

PolyQ diseases are a group of rare neurodegenerative disorders of which there are nine known types: Huntington’s disease (HD); six spinocerebellar ataxias (SCA) types 1, 2, 3, 6, 7, 17; dentatorubral pallidoluysian atrophy (DRPLA); and spinal and bulbar muscular atrophy (SBMA).21

The incidence of polyQ disorders is around 1–10 cases per 100,000 people,21,22 with HD and SCA3 having the highest occurrence worldwide (Table 1).23,24 DRPLA is predominantly documented in Japan25, while the highest frequencies of SBMA have been reported in Finland.26,27 Although each disease is considered rare, together, polyQ diseases constitute the largest group of neurodegenerative disorders that are caused by a single gene.28

<table>
<thead>
<tr>
<th>PolyQ disease</th>
<th>Mutated protein</th>
<th>Frequency worldwide</th>
<th>Clinical features/manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>Huntingtin</td>
<td>3–7/100,000</td>
<td>chorea, progressive cognitive decline, psychiatric disorders</td>
</tr>
<tr>
<td>SCAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA1</td>
<td>Ataxin 1</td>
<td>1–2/100,000</td>
<td>pyramidal signs, peripheral neuropathy, motor control decline</td>
</tr>
<tr>
<td>SCA2</td>
<td>Ataxin 2</td>
<td>Unknown, common in Cuba — 40/100,000</td>
<td>slow eye movement, neuropathy, hyporeflexia, tremor, chorea</td>
</tr>
<tr>
<td>SCA3 (Machado-Joseph disease)</td>
<td>Ataxin 3</td>
<td>1–9/100,000</td>
<td>bulging eye, spasticity, fasciculations, sensory loss, amyotrophy, ataxia</td>
</tr>
<tr>
<td>SCA6</td>
<td>CACNA1 P/Q-type α 1A</td>
<td>0.02–0.31/100,000</td>
<td>pure cerebellar signs</td>
</tr>
<tr>
<td>SCA7</td>
<td>Ataxin 7</td>
<td>&lt;1/100,000</td>
<td>retinal degeneration</td>
</tr>
<tr>
<td>SCA17</td>
<td>TATA-binding protein</td>
<td>0.16/100,000</td>
<td>dystonia, dementia, involuntary movements, hyperreflexia</td>
</tr>
<tr>
<td>DRPLA (Haw River syndrome)</td>
<td>Atrophin 1</td>
<td>2.7/100,000</td>
<td>ataxia, myoclonic epilepsy, choreoathetosis, cognitive deficits</td>
</tr>
<tr>
<td>SBMA (Kennedy disease)</td>
<td>Androgen receptor</td>
<td>1–2/100,000 male</td>
<td>weakness, muscular atrophy, bulbar palsy</td>
</tr>
</tbody>
</table>

Table 1. PolyQ repeat expansion diseases.1,23–25,29–37

All of these conditions are characterized by a specific genetic abnormality that occurs in a unit called a cytosine-adenine-guanine (CAG) trinucleotide repeat, leading to the production of proteins with an expanded polyglutamine tract.26 The resulting proteins are faulty, and the affected proteins differ between polyQ diseases in terms of their function and location within the cell. Moreover, different brain regions and neuronal cell subtypes are affected in each polyQ disease.26 These genetic abnormalities mainly affect the central nervous system and are associated with progressive degeneration, dysfunction, and the death of specific populations of neurons.21,26,27,38,39

As the most common polyQ disorder, the pathological mechanism of HD has been defined. HD is caused by a polyQ expansion in huntingtin protein, an important signal regulator in the nervous system. The primary hallmark is severe deterioration of a section of the brain called the striatum, which is reduced to a fraction of its original size (Figure 5).40

Figure 5. Pathological hallmarks of HD.41
Landscape analysis of neurodegenerative disease research

Journal and patent activity

Currently, there are over 300,000, 220,000, and 50,000 scientific publications (mainly journal articles and patents) related to AD, PD, and polyQ disorders in the CAS Content Collection, respectively. There has been a steady growth of these documents over the last few decades, with a 25–30% increase in the last three years across the three disease subtypes (Figure 6A–F). Journal articles largely dominate, showcasing the intense research in the area.

Figure 6. Yearly trend of the number of documents (journal articles and patents) related to AD, PD and polyQ diseases (A, C and E). Comparison between relative growth in the number of documents around each specific condition (dark blue bars) and all neurodegenerative diseases (light blue bars) in the CAS Content Collection (B, D and F). Orange and yellow lines compare the journal/patent ratio for the specific condition to the journal/patent ratio for all neurodegenerative diseases, respectively. JRN, journal; PAT, patent; JRN/PAT, journal/patent ratio.
Leading countries/regions

The United States, Japan, China, the United Kingdom, and Germany are among the leaders with respect to the number of published journal articles and patents related to AD, PD, and polyQ disorders. A significant proportion of patents come from the United States across all three conditions (Figure 7).

![Figure 7. Top countries/regions with respect to the percentage of AD (A), PD (B), and polyQ-related (C) journal articles (left) and patents (right) in the CAS Content Collection.](image-url)
The journals and institutions with the highest number of published articles across AD, PD, and polyQ disorders are shown in Table 2. Patenting activity in the field of neurodegenerative disorders is dominated by corporate players as compared to academics; the leading organizations with regard to patent activity are also presented in Table 2.

### Publication activity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Leading institutions</th>
<th>Leading journals</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>The Alzheimer’s Disease Neuroimaging Initiative, University of California, Harvard Medical School, Chinese Academy of Sciences</td>
<td><em>Journal of Alzheimer’s Disease</em>, <em>Neurobiology of Aging</em>, <em>Neurology</em>, <em>PLoS One</em></td>
</tr>
<tr>
<td>PD</td>
<td>The National Institutes of Health, Capital Medical University, University of California, Juntendo University School of Medicine, University of Cambridge</td>
<td><em>Movement Disorders</em>, <em>Parkinsonism &amp; Related Disorders</em>, <em>Neurology</em>, <em>PLoS One</em></td>
</tr>
<tr>
<td>PolyQ</td>
<td>University of British Columbia, Massachusetts General Hospital, University of California, University of Cambridge</td>
<td><em>Human Molecular Genetics</em>, <em>Movement Disorders</em>, <em>PLoS One</em>, <em>Neurology</em></td>
</tr>
</tbody>
</table>

### Patenting activity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Commercial organizations</th>
<th>Non-commercial organizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Hoffmann-La Roche, AstraZeneca, Merck (MSD), Pfizer</td>
<td>University of California, French National Center for Scientific Research, Korea Institute of Science and Technology</td>
</tr>
<tr>
<td>PD</td>
<td>Hoffmann-La Roche, AstraZeneca, Merck, Neurosearch, Pfizer</td>
<td>University of California, French National Center for Scientific Research, Korea Institute of Science and Technology, Massachusetts General Hospital, Johns Hopkins University</td>
</tr>
<tr>
<td>PolyQ</td>
<td>Hoffmann-La Roche, AstraZeneca, Merck, Pfizer</td>
<td>University of California, General Hospital Corporation, Harvard College</td>
</tr>
</tbody>
</table>

Table 2. Leading organizations in the field of neurodegeneration in terms of number of published journal articles and patents.
While there is currently no cure for any neurodegenerative conditions, various interventions can help manage symptoms and support overall well-being. Treatment and management approaches to neurodegenerative disorders aim to alleviate symptoms, slow down disease progression, and improve the quality of life for individuals affected by the condition.

There are a variety of medications that are approved by the U.S. Food and Drug Administration for the treatment of neurodegenerative disorders, with many more in late-stage clinical trials. A number of non-pharmacological strategies, such as regular physical activity, a balanced diet, healthy sleep habits, and cognitive-behavioral therapy, have also been suggested to alleviate certain symptoms of neurodegenerative diseases.

**Pre-clinical development and clinical trials**

Over the last 20 years, nearly 2,300 clinical trials have been registered on clinicaltrials.gov for AD, around 1,000 for PD, and about 480 for polyQ diseases. Evaluation of therapeutic clinical trials in the AD, PD, and polyQ settings has revealed that the majority of trials are not phased.

There are around 325 and 250 agents in preclinical development for AD and PD, respectively, which can broadly be categorized as small molecules, antisense oligonucleotides, gene therapy, RNA inhibitor agents, monoclonal antibodies, and cell therapies. Clinical trials are currently dominated by small molecules and monoclonal antibodies.

Almost 45 substances are being researched and developed preclinically for the treatment of polyQ diseases. The vast majority of these are for the treatment of HD, but substances for the treatment of SCA are also in the development pipeline. A wide range of therapies are being investigated, including small molecules, protein degraders, RNA therapeutics, gene therapy, and cell therapies, amongst others.

**Figure 8.** Number of clinical trials per year for AD (A), PD (B), and polyQ disorders (C).
Old tools for new tasks: The potential for drug repurposing in neurodegenerative disease

Since there is no cure for neurodegenerative diseases, drug repurposing studies have been intensely searching to identify existing drugs that could be repositioned to treat conditions like AD and PD. As the pharmaceutical development process is both time-consuming and costly, drug repurposing provides a chance to accelerate it by exploring the neurodegeneration-related effects of agents approved for other disorders. For AD alone, there are 50 widely discussed drugs for AD repurposing; some examples of drugs commonly considered for repurposing to AD and PD are shown in Table 3.

<table>
<thead>
<tr>
<th>Drug</th>
<th>CAS Registry Number®</th>
<th>Original indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>7439-93-2</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>Metformin</td>
<td>657-24-9</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Risperidone</td>
<td>106266-06-2</td>
<td>Antipsychotic</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>98-92-0</td>
<td>Vitamin</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>134523-00-5</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>10540-29-1</td>
<td>Anti-cancer</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>104987-11-3</td>
<td>Immunologic prophylaxis</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>1972-08-3</td>
<td>Appetite stimulant, antiemetic</td>
</tr>
<tr>
<td>Riluzole</td>
<td>1744-22-5</td>
<td>Neurologic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>CAS Registry Number®</th>
<th>Original indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>141758-74-9</td>
<td>Type II diabetes</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>144701-48-4</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Triflusal</td>
<td>322-79-2</td>
<td>Thromboembolic prophylaxis</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>102767-28-2</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>68-19-9</td>
<td>Vitamin B12 deficiencies</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>19171-19-8</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Exemestane</td>
<td>107868-30-4</td>
<td>Breast cancer, postmenopausal</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>163521-12-8</td>
<td>Antidepressant</td>
</tr>
</tbody>
</table>

Table 3. Examples of drugs commonly considered for repurposing to AD and PD.

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**AD**

**PD**
Hot topics in neurodegenerative research

Aging is the most widely explored concept in AD and PD, while pathogenesis, molecular mechanisms, and the clinical manifestations of diseases are the areas attracting the most attention in the polyQ setting (Figures 9 and 10).

**Figure 9.** Key concepts related to AD (A) and PD (B) explored in the scientific publications found in the CAS Content Collection.

**Figure 10.** Conceptual mind map of the polyQ disease research area with indications of the number of documents in each subcategory.
Aging is characterized by a time-dependent gradual accumulation of cell damage and continual physiological functional decline. As such, it is also the most profound risk factor for many diseases. Neurodegenerative diseases, such as AD, PD, and HD, as well as sensory dysfunctions, all increase considerably upon aging.\textsuperscript{56–59}

With an increasing global aging population and the subsequent burden of healthcare for people with age-related diseases, intense efforts have been put forth to understand and prevent the effects of aging. The major cellular and molecular hallmarks of aging have been identified, and their relationships to age-related diseases, and especially to AD as one of the most common neurodegenerative disorders, have been explored (Figure 11).\textsuperscript{60}

**Targeting the hallmarks of aging could help to combat neurodegeneration**

With an increasing global aging population and the subsequent burden of healthcare for people with age-related diseases, intense efforts have been put forth to understand and prevent the effects of aging. The major cellular and molecular hallmarks of aging have been identified, and their relationships to age-related diseases, and especially to AD as one of the most common neurodegenerative disorders, have been explored (Figure 11).\textsuperscript{60}

![Diagram of aging hallmarks and Parkinson's disease hallmarks](image)

Figure 11. Correlation between primary aging hallmarks and AD as reflected by their co-occurrence in the documents in the CAS Content Collection (A). Intersection between PD hallmarks and the hallmarks of aging (B).
Biomarkers

Biomarkers are objective measures that can be used to detect, diagnose, monitor disease progression, assess treatment response, and predict outcomes in individuals with a specific condition. Biomarkers are the fastest-growing concept related to AD, and there is significant interest in establishing reliable biomarkers in PD and polyQ diseases.

Biomarker strategies for PD and polyQ diseases include:

- **Clinical biomarkers**: Motor symptoms and non-motor symptoms
- **Neuroimaging biomarkers**: Dopamine transporter imaging and functional and structural magnetic resonance imaging (MRI)
- **Cerebrospinal fluid biomarkers**: α-Synuclein, tau, and phosphorylated tau
- **Blood-based biomarkers**: Blood-based assays for α-synuclein levels and post-translational modifications, biomarkers of neuroinflammation
- **Genetic biomarkers**: Genetic variants associated with PD risk, identified through genome-wide association studies (GWAS) and next-generation sequencing; pathogenic monogenic mutations in genes such as SNCA, LRRK2, PARK2, and GBA
- **Peripheral biomarkers**: Olfactory dysfunction, alterations in gut microbiota composition and metabolites

- **Mutant protein aggregates**
- **Cerebrospinal fluid biomarkers**: Tau, neurofilament light chain, and specific fragments of huntingtin protein in HD
- **Peripheral biomarkers**: Mutant protein fragments, microRNAs, molecular signs of oxidative stress
- **Neuroimaging markers**: Structural changes in the brain using MRI
- **Electrophysiological markers**: Changes in electrical activity in the brain or periphery
- **Biomarkers of oxidative stress and inflammation**: Markers of lipid peroxidation, cytokine levels, or markers of glial activation
- **Metabolic biomarkers**: Markers of energy metabolism, mitochondrial function, or metabolite levels in the brain or peripheral tissues
- **Genetic modifiers**: GWAS or whole-genome sequencing

The biomarkers of particular interest in AD, as determined using insights from the CAS Content Collection, are highlighted in Figure 12.

![Figure 12. AD biomarkers as represented in the CAS Content Collection.](image-url)
Summary and future directions

The vast global impact combined with the incurable nature of neurodegenerative disorders presents us with a need for well-directed research. In response to this, investigation into neurodegenerative disorders is an active and evolving field. Although there are a number of distinct conditions, there are common areas of interest for future research efforts across the board. Key areas for research in AD, PD, and polyQ disorders are depicted in Figure 13.

Figure 13. Future research directions in the field of neurodegeneration research by disease classification.

While significant challenges remain in the fight against neurodegeneration, sustained efforts in research, advocacy, and care have the potential to improve outcomes for affected individuals and advance our collective efforts toward a future without neurodegenerative diseases.
References


For more details on the research landscape of neurodegeneration, see our publication at http://link.cas.org/neurodegenerative
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