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Review

Advancements in neurodegenerative diseases: Pathogenesis and novel neurorestorative interventions

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ABSTRACT

Progressive neurodegenerative diseases (NDs) that lack effective disease-modifying treatments, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), represent significant global health challenges. In recent years, key research findings have included the role of neuroinflammation driven by microglia and astrocytes, the impact of genetic mutations, and the importance of autophagy and mitochondrial quality control in maintaining neuronal health. In this review, we summarize recent advancements of the pathogenesis of NDs, the cellular and animal models that have provided valuable insights into disease mechanisms, and the development of blood-based biomarkers for early diagnosis and monitoring of disease progression. We also highlight emerging neurorestorative therapeutic strategies involving stem cell therapy, antisense oligonucleotides, and induced pluripotent stem cells. Additionally, we cover recent clinical trials of promising drugs, such as lecanemab and donanemab for AD, and tavapadon for PD. Finally, we propose future research directions, emphasizing the need for combination therapies that target multiple pathways, the development of more precise animal models, and the integration of nanotechnology for improved drug delivery across the blood–brain barrier.

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1. Introduction

Neurodegenerative diseases (NDs), including Alzheimer's disease (AD) and Parkinson's disease (PD), are among the most prevalent neurological disorders affecting middle-aged and older individuals. These diseases are characterized by progressive neuronal loss and dysfunction that lead to severe impairments in cognition and movement. Current research indicates that the etiology of NDs involves multifactorial combinations of genetic mutations, environmental exposures, and intracellular signaling abnormalities.[1,2]

Currently, one of the critical areas of research focus is the role of neuroinflammation in the pathogenesis of NDs. Neuroinflammation, primarily driven by the activation of microglia and astrocytes, has been implicated in the progression of various neurodegenerative conditions. Dysregulated immune responses and chronic inflammation can also exacerbate neuronal damage,

Abbreviations: MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-Hydroxydopamine; AD, Alzheimer's disease; Aβ, Amyloid-beta; ALS, Amyotrophic lateral sclerosis; ASOs, Antisense oligonucleotides; BBB, Blood–brain barrier; CNS, Central nervous system; CRISPR, Clustered regularly interspaced short palindromic repeats; ER, Endoplasmic Reticulum; HD, Huntington's disease; iPSC, Induced pluripotent stem cell; MAO, Monoamine Oxidase; MS, Multiple sclerosis; PD, Parkinson's disease; PPAR, Peroxisome proliferator-activated receptor; PDI, Protein Disulfide Isomerase; ROS, Reactive oxygen species; SNpc, Substantia nigra pars compacta.

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suggesting that targeting these pathways could be a promising therapeutic approach for neurorestoration.[3,4]

Furthermore, the interplay between genetic and environmental factors in modulating neuroinflammatory responses has garnered significant attention. For instance, exposure to environmental toxins, such as heavy metals and pesticides, has been linked to increased risk of developing NDs, highlighting the importance of addressing these modifiable risk factors. Additionally, genetic predispositions, including mutations in the apolipoprotein E (*APOE*) gene in AD and the leucine-rich repeat kinase 2 (*LRRK2*) gene in PD, further complicate the disease landscape, necessitating a comprehensive approach to understanding and treating these disorders.[1–3]

Based on data from the World Health Organization, about 50 million people worldwide were living with NDs in 2019, and this number is expected to increase to 152 million by 2050. Although these diseases are found across all age groups and geographic regions, their incidence significantly increases with age. For example, in Europe, the overall prevalence of dementia caused by NDs in the 65–69-year age group is 1.6%, while that in the 85–89-year age group jumps to 11%.[5,6]

According to the latest data from the Global Burden of Disease Study (GBD 2021), neurological conditions have become the leading cause of disease burden globally. Their key findings include the following.

In 2021, approximately 3.4 billion people (43.1% of the global population) were affected by neurological conditions.[2,4] Neurological conditions caused 443 million disability-adjusted life years (DALYs) in 2021, surpassing cardiovascular diseases as the top contributor to the global disease burden.[2,4] Since 1990, the total number of DALYs due to neurological conditions has increased by 18.2%. In 2021, neurological conditions resulted in 11.1 million deaths.[2,4]

High-income countries have a relatively low burden of neurological conditions, accounting for about 10% of the global burden. Low and middle-income countries bear over 90% of the neurological disease burden and 84% of related deaths,[2,4] while high-income countries have 70 times more neurological professionals per 100,000 people compared with low-income countries.[2,4]

In 2021, the top 10 neurological conditions contributing to the disease burden were stroke, neonatal encephalopathy, migraine, AD and other dementias, diabetic neuropathy, meningitis, epilepsy, neurological complications due to preterm birth, autism spectrum disorder, and nervous system cancers.[2,4] Diabetic neuropathy has seen the fastest growth since 1990, with 206 million cases in 2021.[2,4]

GBD 2021 emphasizes the importance of strengthening public health measures, including prevention, early diagnosis, and comprehensive treatment, to address the growing burden of neurological diseases, especially in developing countries.[2,4]

In this review, we summarize the latest advancements in the understanding of the pathogenesis of NDs and explore potential neurorestorative mechanisms. By examining the intricate molecular and cellular processes involved, we hope to provide new insights that will lead to innovative therapeutic strategies for these debilitating conditions. This comprehensive overview covers the role of neuroinflammation, the impacts of genetic and environmental factors, and emerging therapeutic approaches, all of which may ultimately contribute to the development of effective treatments for NDs.[1–4]

2. Laboratory research in NDs

2.1. AD

AD is a progressive ND that primarily affects older adults, leading to cognitive decline, memory loss, and behavioral changes. It is the most common cause of dementia, accounting for 60%–80% of all dementia cases worldwide. The disease is characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein in the brain, which disrupt neuronal function and lead to cell death.[7,8]

2.1.1. Role of microglia in AD

The protective role of microglia in AD is widely supported by experimental data. Microglia are the primary immune cells of the central nervous system (CNS), responsible for clearing protein debris in brain and responding to inflammation. Studies have shown that microglia play a protective role by promoting the clearance of Aβ plaques and tau protein aggregates. Additionally, the activation state of microglia is closely related to the progression of AD, indicating that their role in the disease process may change over time and at different stages of the disease. Dysfunction of microglia is also closely associated with the onset and progression of various NDs. For example, the interleukin-3 signaling molecule has been identified as a key mediator in the crosstalk between astrocytes and microglia, helping to improve the inflammatory response and immune system function of the body, thereby protecting against AD.[9,10]

Recent studies have revealed more complex roles of microglia in AD. Microglia not only play a role in clearing Aβ plaques, they also have important functions in regulating neuroinflammation and neuronal survival. Specifically, different activation states of microglia (e.g., M1 and M2) may have different impacts at various stages of AD. M1 microglia primarily produce proinflammatory factors, which may exacerbate neuronal damage, while M2 microglia have anti-inflammatory and neuroprotective effects.[9,10]

2.1.2. Role of autophagy in AD

Autophagy dysfunction is a key factor in the aggregation of Aβ and tau proteins in AD. Autophagy is an important cellular defense and protection mechanism that maintains cellular homeostasis by clearing abnormally accumulated proteins and damaged organelles. Studies have shown that autophagy-promoting drugs, such as pituitary adenylate cyclase-activating polypeptide, have the potential to alleviate cognitive impairment in animal models. This finding underscores the importance of autophagy in maintaining neuronal survival and provides possible targets for developing new therapeutic strategies.[7,9,11–14]

Furthermore, natural compounds, including curcumin, have been found to alleviate AD pathology by modulating the autophagy pathway. Curcumin reduces neuronal damage by inhibiting the Toll-like receptor 4/nuclear factor-kB signaling pathway and has shown protective effects on cognitive function in AD rats.[7,9,11–14]

2.1.3. Advances in animal models

Animal models of AD are crucial tools for elucidating disease mechanisms and evaluating therapeutic strategies. By expressing human gene variants associated with AD, such as *APOEε4*, in mice, researchers can simulate the genetic risk factors of AD. The development and use of such models provide new platforms for studying the molecular mechanisms of AD and screening potential drugs. For example, using the amyloid precursor protein (APP)/presenilin 1 (PS1) double transgenic mouse model, researchers can simulate the neurobehavioral manifestations and typical morphological changes of AD, including senile plaques, neurofibrillary tangles, and amyloid deposits, through intraperitoneal injection of aluminum compounds. These models play important roles in drug screening and mechanistic studies.[15–19]

New transgenic and gene knockout technologies (e.g., clustered regularly interspaced short palindromic repeats [CRISPR]) have enabled researchers to create more precise AD models. Compared

with previous models, these new models better simulate the pathological features of AD but can also be used to screen new therapeutic drugs. For example, the new five familial AD transgene (5xFAD) mouse model, which carries multiple AD-related gene mutations, exhibits a more comprehensive pathological process of AD.[15–19]

2.1.4. Development of blood biomarkers

Blood biomarkers hold significant potential for the early diagnosis and monitoring of AD. Studies have shown that plasma levels of phosphorylated tau protein (p-tau) are closely related to the severity of AD and may become an important indicator for early diagnosis. Additionally, detecting the presence of brain amyloid and reactive astrocyte biomarkers in the blood are currently the best screening methods for identifying patients most likely to develop AD.[8,20,21]

Apart from p-tau, research on blood biomarkers also includes changes in other proteins and lipids. For example, changes in blood levels of phospholipids and sphingolipids may reflect CNS lipid metabolism disorders and neuronal degeneration, which can be detected in the early stages of AD. New high-sensitivity detection technologies make early diagnosis of AD possible. Studies have shown that the plasma Aβ42/40 ratio and p-tau protein levels can serve as early diagnostic indicators of AD. Furthermore, new research has found that blood levels of neurofilament light chain (NFL) protein and glial fibrillary acidic protein are also closely related to the progression of AD, and thus can be used to monitor disease progression and treatment effects.[8,20,21]

2.2. PD

PD is a progressive ND characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the presence of Lewy bodies, which are intracellular inclusions containing aggregates of α-synuclein. PD is the second most common ND, affecting about 1% of individuals over the age of 60 years. Despite extensive research, the exact pathogenesis of PD remains elusive. This part aims to provide a comprehensive overview of recent advances in cellular, animal, and bioinformatics studies related to PD, focusing on molecular mechanisms, genetic factors, and potential biomarkers.

2.2.1. Cellular mechanisms

The hallmark of PD is the selective degeneration of dopaminergic neurons in the SNpc, which leads to a significant reduction in dopamine levels in the striatum. The following cellular mechanisms have been implicated in this process.

2.2.1.1. Oxidative stress. Dopaminergic neurons are particularly susceptible to oxidative stress caused by high levels of dopamine metabolism, which generate reactive oxygen species (ROS). The accumulation of ROS can damage cellular components, leading to neuronal death. Studies have shown that oxidative stress plays a crucial role in the pathogenesis of PD by damaging lipids, proteins, and DNA within neurons.[22,23]

2.2.1.2. Mitochondrial dysfunction. Mitochondria play crucial roles in energy production and cellular homeostasis. In PD, mitochondrial dysfunction is a significant contributor to neuronal death. Mutations in certain genes involved in mitochondrial function, such as *PINK1, LRRK2* and *Parkin*, have been linked to familial forms of PD. These mutations impair the process of mitophagy, leading to the accumulation of damaged mitochondria and increased oxidative stress.[24,25]

2.2.1.3. Protein aggregation. The accumulation of misfolded proteins, particularly α-synuclein, is a key feature of PD. Such aggregates form Lewy bodies and contribute to cellular toxicity. Impaired autophagy and proteasomal degradation pathways are thought to play a role in the accumulation of these protein aggregates. The aggregation of α-synuclein disrupts cellular functions, including vesicle trafficking and synaptic function, ultimately leading to neuronal death.[26,27]

2.2.1.4. Endoplasmic reticulum (ER) stress. The accumulation of misfolded proteins in the ER can trigger the unfolded protein response, leading to ER stress and apoptosis, and has been implicated in the pathogenesis of PD. ER stress can result from the accumulation of α-synuclein aggregates, which interfere with normal protein folding and processing within the ER.[28,29]

2.2.1.5. Neuroinflammation. Activated microglia and astrocytes release proinflammatory cytokines and other neurotoxic factors, contributing to the degeneration of dopaminergic neurons. Chronic neuroinflammation is a common feature in the brains of PD patients. The sustained activation of glial cells can exacerbate neuronal damage through the release of inflammatory mediators and ROS.[30,31]

2.2.1.6. Genetic factors. Genetic mutations play a significant role in the pathogenesis of both familial and sporadic PD. The following genes have been identified that are associated with an increased risk of developing PD.

2.2.1.7. α-Synuclein (SNCA). Mutations and multiplications in *SNCA* lead to the overproduction and aggregation of α-synuclein, forming Lewy bodies. The A53T mutation in *SNCA* was the first identified genetic cause of PD. These mutations result in the production of misfolded α-synuclein, which aggregates and disrupts cellular functions.[32,33]

2.2.1.8. LRRK2. Mutations in *LRRK2* are the most common genetic cause of familial PD. *LRRK2* is a kinase involved in various cellular processes, including autophagy and mitochondrial function. The G2019S mutation is the most prevalent and has been linked to increased kinase activity and neuronal toxicity. *LRRK2* mutations can lead to the dysregulation of multiple cellular pathways, contributing to neurodegeneration.[34,35]

2.2.1.9. PINK1 and Parkin. These genes are involved in mitochondrial function. Mutations in *PINK1* and *Parkin* lead to impaired mitophagy, resulting in the accumulation of damaged mitochondria and increased oxidative stress. The *PINK1* and *Parkin* proteins work together to identify and degrade damaged mitochondria, and mutations in their coding genes disrupt this process, leading to cellular dysfunction.[29,36]

2.2.1.10. DJ-1. DJ-1 is involved in protecting cells from oxidative stress. Mutations in *DJ-1* impair its protective function, making neurons more susceptible to oxidative damage. *DJ-1* acts as a sensor for oxidative stress and helps to regulate antioxidant responses, and its dysfunction can exacerbate oxidative damage in neurons.[31,37]

2.2.1.11. VPS35. Mutations in *VPS35*, a component of the retromer complex involved in protein sorting, have been linked to PD. These mutations disrupt the trafficking of proteins, leading to cellular dysfunction. *VPS35* mutations can impair the recycling of membrane proteins and receptors, contributing to neuronal degeneration.[38,39]

2.2.2. Animal models

Several models have been developed to mimic the key features of PD.

2.2.2.1. 6-Hydroxydopamine (6-OHDA) model. This Rodent model involves the injection of 6-OHDA, a neurotoxin, into the nigrostriatal pathway, leading to the selective degeneration of dopaminergic neurons. This model is widely used to study the motor symptoms of PD and to test neuroprotective strategies. The 6-OHDA model replicates the loss of dopaminergic neurons and the resulting motor deficits, making it a valuable tool for PD research.[40–43]

2.2.2.2. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. MPTP is a neurotoxin that selectively targets dopaminergic neurons. MPTP-treated mice and non-human primates exhibit many of the motor and non-motor symptoms of PD, making this model valuable for research on disease mechanisms and potential treatments. The MPTP model is particularly useful for studying neurodegenerative processes and testing neuroprotective therapies.[44–47]

2.2.2.3. Genetic models. Transgenic mice that express mutant forms of PD-related genes, such as *SNCA*, *LRRK2*, *PINK1*, and *Parkin*, have also been developed. These models have helped to elucidate the role of specific genetic mutations in the pathogenesis of PD and have led to the identification of potential therapeutic targets. Genetic models also replicate various aspects of PD pathology, including protein aggregation and mitochondrial dysfunction.[48–50]

2.2.2.4. Non-human primate models. Because of their close anatomical and physiological similarities to humans, non-human primates, such as macaques, are used to study PD. MPTP-treated primates exhibit many of the motor and non-motor symptoms of PD, making them valuable for preclinical testing of new therapies. These models are particularly useful for studying complex motor behaviors and testing the efficacy of potential treatments in a system that closely resembles human PD.[48,51]

2.2.3. Bioinformatics and biomarkers

2.2.3.1. Transcriptomics and proteomics. High-throughput technologies, such as RNA sequencing (RNA-seq) and mass spectrometry, have been used to identify differentially expressed genes and proteins in PD. These studies have revealed alterations in various biological pathways, including those related to mitochondrial function, protein degradation, and immune response. Transcriptomic and proteomic analyses can provide insights into the molecular changes associated with PD and identify potential therapeutic targets.[48,50]

2.2.3.2. Metabolomics. Metabolomics studies have identified changes in metabolic pathways in PD patients. For example, alterations in lipid metabolism and energy production have been observed. These findings provide insights into the metabolic dysregulation associated with PD and may lead to the identification of novel biomarkers. Metabolomic profiling can help to identify specific metabolic changes that occur in PD, which may serve as early indicators of the disease.[48,50]

2.2.4. Biomarker discovery

The identification of reliable biomarkers for PD is crucial for early diagnosis, monitoring of disease progression, and evaluation of therapeutic efficacy. The following potential biomarkers have been identified.

2.2.4.1. α-Synuclein. Elevated levels of α-synuclein in cerebrospinal fluid (CSF) and blood have been proposed as biomarkers for PD. However, the sensitivity and specificity of α-synuclein as a biomarker are still under investigation. α-Synuclein levels can reflect the presence of Lewy body pathology, which may serve as a marker for disease progression.[48,50]

2.2.4.2. NFL. NFL is a structural protein found in neurons. Elevated levels of NFL in CSF and blood have been associated with neurodegeneration and may serve as a biomarker for PD. NFL levels also indicate the extent of neuronal damage and may be useful for monitoring disease progression.[48,50]

2.2.4.3. DOPA decarboxylase (DDC). DDC levels in CSF have been shown to differentiate PD patients from controls with high accuracy. DDC is involved in dopamine synthesis, and its levels reflect dopaminergic dysfunction. Measuring DDC levels can thus help to assess the integrity of the dopaminergic system in PD patients.[48,50]

2.2.4.4. LRRK2 activity. Increased kinase activity of *LRRK2* has been observed in some patients with idiopathic PD. Blood-based assays to measure *LRRK2* activity may help stratify patients and guide personalized treatment. *LRRK2* activity can provide insights into the underlying molecular mechanisms of PD and may serve as a target for therapeutic intervention.[48,50]

2.2.4.5. Metabolite-based biomarkers. Metabolomics studies have identified several metabolites, including salsolinol and 1,2-dihydroxybenzene, as potential biomarkers for PD. These metabolites are involved in dopamine metabolism and oxidative stress. Metabolite profiling can help to identify specific biochemical changes associated with PD, which may serve as early indicators of the disease.[48,50]

2.3. Amyotrophic lateral sclerosis (ALS)

ALS is a devastating ND characterized by the progressive loss of motor neurons in the brain and spinal cord that lead to muscle weakness, paralysis, and ultimately death. Despite extensive research, the exact mechanisms underlying ALS pathogenesis remain elusive, and there is currently no cure.

2.3.1. Cellular models of ALS

2.3.1.1. Tar-DNA binding protein of 43 kDa (TDP-43) pathology. TDP-43, a major pathological protein in ALS, is found in aggregates within the cytoplasm of affected neurons. Studies have shown that TDP-43 undergoes post-translational modifications, such as hyperphosphorylation, ubiquitination, and cleavage, which contribute to its aggregation and toxicity. Cellular models have been instrumental in elucidating the mechanisms of TDP-43 pathology. For instance, hyperphosphorylation of TDP-43 by casein kinase 1δ has been shown to reduce its phase separation and aggregation, suggesting a protective role against TDP-43 toxicity.[52]

2.3.1.2. Nucleocytoplasmic transport deficits. Deficits in nucleocytoplasmic transport have been implicated in ALS pathogenesis. Using CRISPR-Cas9 technology, researchers have developed cell lines that express fluorophore-tagged proteins to study the transport pathways affected by ALS-associated peptides. These models have revealed that certain peptides, such as poly-PR, disrupt nucleocytoplasmic transport, contributing to cellular dysfunction.[53,54]

2.3.1.3. Oxidative stress and DNA damage. Oxidative stress is a well-documented feature of ALS. In motor neurons, elevated levels of ROS lead to DNA damage and activation of DNA damage response proteins, such as p53bp1 and γH2ax. Cellular experiments using ROS scavengers have demonstrated a reduction in DNA damage,

highlighting the potential therapeutic benefits of targeting oxidative stress in ALS.[55]

2.3.1.4. Protein disulfide isomerase (PDI) activity. Recent studies have highlighted the role of PDI in ALS. PDI is involved in the formation and rearrangement of disulfide bonds in proteins, and its redox activity has been shown to inhibit ALS phenotypes in cellular models. For example, PDI overexpression in cellular models of ALS has been found to reduce the aggregation of misfolded proteins and improve cell viability, suggesting its potential as a therapeutic target.[56]

2.3.1.5. APP interaction. The interaction between mutant superoxide dismutase 1 (SOD1) and APP has been studied in cellular models of ALS. Research has shown that mutant SOD1 increases APP expression and phosphorylation, leading to enhanced β-secretase cleavage. This interaction appears to play a significant role in the pathology of ALS.

A study using fluorescence resonance energy transfer analysis suggested a close interaction between SOD1 and APP at hippocampal synapses. Notably, the SOD1(G93A) mutation was found to induce APP−SOD1 conformational changes, indicating crosstalk between these two signaling proteins.

Researchers have explored potential therapeutic approaches targeting this interaction. Inhibition of APP processing via a monoclonal antibody called BBS, which blocks the β-secretase cleavage site of APP, has shown promising results. This intervention resulted in the following results: reduction of mutant SOD1(G93A) levels in both animal and cellular models of ALS; significant prolongation of life span in SOD1(G93A) mice; diminished inflammation; and reductions in the levels of APP, its processing product soluble APPβ, and pro-apoptotic p53. These findings suggest that APP and its processing products contribute to ALS pathology through several different pathways. The use of monoclonal antibodies to inhibit APP processing, which has been shown to reduce mutant SOD1 levels and improve cell survival, represents a potential therapeutic approach for ALS.[57]

2.3.2. Animal models of ALS

2.3.2.1. TDP-43 and SOD1 models. Transgenic TDP-43 and SOD1 animal models have played a crucial role in elucidating the pathogenesis of ALS. These models replicate many important features of human ALS, providing valuable insights into disease mechanisms and potential therapeutic targets.

TDP-43 transgenic mice exhibit the following characteristics: dose-dependent degeneration of cortical and spinal motor neurons, leading to ALS-like spastic quadriplegia; presence of ubiquitinated and phosphorylated TDP-43 aggregates in neuronal cytoplasm and nuclei, which is a pathological hallmark of ALS patients; presence of distinctive ~25-kDa C-terminal fragments in nuclear fractions at levels that correlate with disease progression, suggesting a possible gain of aberrant nuclear function; and, in addition to motor neuron degeneration, non-motor cortical and subcortical neuronal degeneration characteristic of frontotemporal lobar degeneration.[58–60]

SOD1 transgenic mice, particularly the G93A mutant line, have been extensively studied, revealing several key pathological mechanisms: mitochondrial dysfunction: impaired mitochondrial function, leading to motor neuron degeneration; axonal transport deficits, namely disruptions in axonal transport that potentially contribute to motor neuron dysfunction; neuromuscular junction (NMJ) abnormalities, highlighting the early involvement of NMJs in ALS pathogenesis and suggesting that NMJ disassembly may be a critical early event in the disease process; and electrophysiological changes, which have revealed alterations in motor neuron membrane properties and responses to excitatory neurotransmitters, providing insights into the functional consequences of the mutation.[61,62]

2.3.2.2. Metabolic dysfunction. ALS is recognized as a systemic disease with significant metabolic dysfunction. Animal models have shown that ALS-affected muscle tissue exhibits elevated energy demands and a switch from glycolysis to fatty acid oxidation. Additionally, increased lipolysis in adipose tissue and impaired glucose homeostasis in the liver and pancreas have been observed. These findings underscore the importance of metabolic pathways in ALS pathogenesis and highlight potential therapeutic targets.[53]

2.3.2.3. ER stress. Chronic ER stress is another hallmark of ALS. Studies using rodent models have demonstrated that the ER-resident protein cerebral dopamine neurotrophic factor (CDNF) can rescue motor neurons from ER stress-induced cell death. CDNF administration in transgenic TDP-43 and SOD1-G93A animal models has been shown to halt disease progression and improve motor function, suggesting its potential as a therapeutic agent.[62]

2.3.3. Genetic animal models

Over the past three decades, numerous genetic animal models related to ALS have been developed in both vertebrates and invertebrates, including yeast, worms, flies, zebrafish, mice, rats, guinea pigs, dogs, and non-human primates. These models have been instrumental in dissecting the pathological mechanisms underlying motor neuron degeneration and ALS progression. For example, zebrafish models have been used to study the effects of genetic mutations on development and function of motor neurons, while mouse models have provided insights into the roles of specific genes in ALS pathogenesis.

2.3.3.1. Immunotherapy approaches. Recent studies have explored the use of immunotherapy in ALS animal models. For instance, human-derived anti-poly-GA antibodies have been tested in cellular and mouse models of C9orf72-associated ALS. These antibodies were found to reduce the number of intracellular poly-GA aggregates and modestly improve behavioral phenotypes in mice, suggesting a potential therapeutic approach for ALS.[63]

2.3.4. Biomarkers in ALS

2.3.4.1. Proteomic approaches. The identification of reliable biomarkers for ALS diagnosis and treatment monitoring is a critical area of research. Proteomic studies have identified several potential biomarkers in human tissues, plasma, CSF, and exosomes. For example, post-translational modifications of TDP-43 and α-synuclein have been proposed as biomarkers for ALS and PD, respectively.[64] Advances in proteomic technologies have enabled the high-throughput quantitation of thousands of proteins, facilitating the discovery of novel biomarkers.[55]

2.3.4.2. MicroRNAs (miRNAs). Recently, miRNAs have emerged as promising biomarkers for ALS. Dysregulation of muscle-specific miRNAs (myomiRs) has been observed in both animal models and human patients with ALS. For instance, miR-206 is upregulated in ALS-affected muscle tissue and serum, suggesting its potential as a non-invasive biomarker for disease progression. Further research is needed to validate these findings and explore the therapeutic potential of targeting miRNAs in ALS.[54]

2.3.4.3. Antioxidant biomarkers. Oxidative stress biomarkers have also been investigated in ALS. A bidirectional Mendelian randomization study explored the causal relationship between antioxidant biomarkers and NDs, including ALS. Although no significant causal evidence was found, the study highlighted the importance of

antioxidant balance in ALS pathogenesis and the potential for antioxidant-based therapies.[65]

2.3.4.4. Blood biomarkers. Blood-based biomarkers offer a non-invasive and accessible means of diagnosing and monitoring ALS. Neurofilaments are among the most studied blood biomarkers in ALS. Changes in neurofilament concentration before or after diagnosis have been shown to aid in prognostication and patient stratification, supporting more efficient and targeted clinical trials. However, technical challenges, such as the matrix effect of blood components, need to be addressed to improve the reproducibility and sensitivity of these assays.[66]

2.3.4.5. Genetic biomarkers. Genetic biomarkers have been identified that may help distinguish various ALS subtypes and inform prognosis. For example, mutations in *C9orf72* are associated with a specific subtype of ALS characterized by the presence of dipeptide repeat proteins. Genetic testing for such mutations can aid in the early diagnosis and personalized treatment of ALS patients.[67]

2.4. Huntington's disease (HD)

HD is a devastating ND characterized by progressively worsening motor, cognitive, and psychiatric disturbances. Cellular and animal models, along with biomarker studies, have provided valuable insights into the pathogenesis of HD and potential therapeutic avenues. In terms of pathological mechanisms, HD is primarily associated with the aggregation of mutant Huntingtin (mHTT) protein and its abnormal interactions, leading to neuronal dysfunction and cell death.

2.4.1. Cellular models

Cellular models have been instrumental in dissecting the molecular underpinnings of HD pathogenesis. Induced pluripotent stem cell (iPSC)-derived neural cells from HD patients have emerged as a powerful tool to study disease-relevant phenotypes in a human cellular context. Bioenergetic deficits, particularly in glycolytic metabolism, have been consistently observed in iPSC-derived HD neurons.[68,69] Proteomics and multiomics analyses further revealed that decreased expression of glycolytic enzymes lead to reduced glycolytic capacity and ATP levels.[68] Interestingly, supplementation with pyruvate or late glycolytic metabolites can rescue ATP levels, suggesting a potential therapeutic strategy targeting glycolytic deficits.[68]

Additionally, cellular models have elucidated the role of protein kinase C (PKC) signaling in HD pathogenesis. Aggregates of mHTT were found to associate with PKC isoforms, including PKCδ, a pro-apoptotic kinase.[70] This association was observed in both cellular and transgenic models, implying a potential link between mHTT aggregation and apoptotic signaling cascades.[70]

2.4.2. Animal models

Transgenic mouse models, such as the R6/2 and YAC128 lines, have been extensively utilized to study the effects of mHTT expression on neuronal function and behavior.

Electrophysiological studies in R6/2 mice revealed that brain-derived neurotrophic factor (BDNF) protected against N-methyl-D-aspartate receptor-mediated excitotoxicity, a proposed mechanism underlying striatal neurodegeneration in HD.[71,72] Notably, this protective effect was shown to be mediated by adenosine A2A receptors, highlighting the potential therapeutic role of BDNF and A2A receptor ligands.[71,72]

In addition to motor deficits, cognitive impairments are a prominent feature of HD. Interestingly, the delivery of ciliary neurotrophic factor prevented both motor and cognitive dysfunction in a quinolinic acid-induced rodent model of HD.[69] This finding underscores the potential of neurotrophic factors in mitigating the diverse symptomatology of HD.

2.4.3. Biomarkers

The identification and validation of reliable biomarkers are crucial for early diagnosis, monitoring disease progression, and evaluating therapeutic responses in HD. Magnetic resonance spectroscopy studies have revealed alterations in brain metabolites, such as N-acetyl aspartate (NAA) and myo-inositol, in individuals with pre-manifest and early HD.[73] Notably, total NAA levels correlated with disease burden scores, suggesting its potential as a biomarker for disease progression.[73]

Recent research has also focused on peripheral biomarkers, which could serve as minimally invasive measures of HD pathology. NFLs and mHTT levels in biofluids have shown promise as potential biomarkers.[74] Additionally, lipoprotein profiles in plasma exhibit significant changes in HD patients, with components of specific lipoprotein subfractions correlating with motor and functional assessments.[74] These findings highlight the potential of peripheral biomarkers for HD diagnosis and monitoring.

2.5. Multiple sclerosis (MS)

MS is a chronic, inflammatory, and demyelinating disease of the CNS, characterized by the formation of lesions, axonal damage, and neurodegeneration. The pathogenesis of MS involves an immune system attack on the CNS, leading to the destruction of myelin and damage to neurons, which in turn triggers inflammation and neurodegenerative processes. Clinical manifestations are diverse and include sensory abnormalities, muscle weakness, ataxia, visual disturbances, and cognitive impairment. Despite significant advances in understanding the disease mechanism and developing therapeutic interventions, MS remains a complex and challenging condition.

2.5.1. Cellular models and experimental approaches

2.5.1.1. Oligodendrocyte (OL) cultures and myelinating Co-cultures. OLs are the myelinating cells of the CNS, and their dysfunction plays a crucial role in the pathogenesis of MS. Primary OL cultures derived from rodent tissues have been instrumental in studying OL biology and demyelinating diseases.[75] Immunomagnetic isolation techniques have facilitated the efficient purification of OL precursor cells from neonatal mouse pups, enabling the generation of enriched OL cultures.[76] These cultures provide a valuable platform for investigating the molecular mechanisms underlying OL development, differentiation, and remyelination processes.

Furthermore, myelinating co-cultures of OLs together with neurons, have emerged as powerful tools for studying myelin formation, maintenance, and repair.[75] Such co-culture systems allow researchers to dissect the complex interactions between OLs, neurons, and other glial cells, shedding light on the pathways involved in demyelination and remyelination.

2.5.1.2. Immune cell cultures and neuroinflammation. MS is considered as an autoimmune disorder, with immune cell infiltration and neuroinflammation playing pivotal roles in disease pathogenesis. Advances in single-cell technologies, such as mass cytometry and single-cell RNA sequencing, have revolutionized our understanding of the immune cell populations involved in MS and its animal models.[77] These techniques have enabled the characterization of cellular heterogeneity, plasticity, and functional states at an unprecedented resolution, providing insights into the contributions of specific immune cell subsets to disease initiation, progression, and recovery.

2.5.2. Animal models of MS

The most commonly used model is experimental autoimmune encephalomyelitis (EAE), which recapitulates many aspects of the human disease.[77–80]

2.5.2.1. EAE. EAE is induced by immunizing animals, typically rodents, with myelin-derived peptides or proteins, leading to the activation of autoreactive T cells and subsequent CNS inflammation and demyelination.[77,78] While acute and relapsing-remitting forms of EAE are suitable for modeling these phases of MS, the secondary progressive EAE stage, which is often refractory to many immune therapies, is better represented in Biozzi ABH mice.[78]

EAE models have provided valuable insights into the roles of various immune cell subsets, such as T helper (Th)1, Th17, and regulatory T cells, in disease initiation and progression.[77] Additionally, these models have facilitated the investigation of potential therapeutic targets and the validation of new treatment strategies.[79,81]

2.5.2.2. Cuprizone model. The cuprizone model for studying demyelination and remyelination processes without the involvement of T cells is gaining in popularity.[78] In this model, administration of the copper chelator cuprizone to mice leads to selective OL death and demyelination, primarily in the corpus callosum.[82] The cuprizone model allows researchers to investigate the mechanisms underlying OL dysfunction, demyelination, and remyelination, as well as the roles of other glial cells, such as microglia and astrocytes, in these processes.

Viral models, such as Theiler's murine encephalomyelitis virus and the neurotropic JHM strain of the murine coronavirus, have also been used to study MS-like pathology.[83] These models provide insights into the interplay among viral infections, immune responses, and demyelination, potentially shedding light on the potential role of environmental factors in MS pathogenesis.

2.5.3. Biomarkers for MS

Several promising biomarkers have emerged from basic research studies, spanning various modalities, including imaging, and body fluid and molecular analyses[84–86].

2.5.3.1. Imaging biomarkers. Magnetic resonance imaging (MRI) has been extensively used in MS research and clinical practice. Recent advancements in diagnostic MRI techniques, such as the detection of central veins within lesions and the incorporation of spinal cord and symptomatic lesions, have the potential to increase diagnostic accuracy.[84,86] In addition, brain volume measurements and lesion counts on T2-weighted and gadolinium-enhanced T1-weighted scans have shown prognostic value and utility in monitoring disease activity and treatment response.[85,86]

Recent studies have demonstrated the potential of optical coherence tomography angiography (OCT-A) as a valuable tool for identifying biomarkers associated with neurodegeneration and vascular changes in MS.[87,88] This non-invasive imaging technique allows for detailed visualization of retinal and optic nerve pathology, offering insights into CNS involvement in MS patients.[89]

OCT-A has revealed significant alterations in the retinal microvasculature in MS patients compared with healthy controls. For instance, studies have shown reduced vessel density in the superficial vascular complex and peripapillary regions in MS patients, with more pronounced reductions observed in those with a history of optic neuritis.[90,91] These vascular changes may reflect underlying neurodegenerative processes and could serve as potential biomarkers for disease progression and severity.[91]

Furthermore, OCT-A measurements have been found to correlate with clinical and paraclinical variables in MS, including visual function, disability status, and MRI findings.[88] This suggests that OCT-A parameters could potentially be used as non-invasive biomarkers for screening, early diagnosis, and monitoring of disease progression in MS.[89,92]

2.5.3.2. Body fluid biomarkers. CSF analysis has yielded several potential biomarkers for MS. Chitinase 3-like 1 and the light subunit of neurofilaments have shown prognostic value in patients with clinically isolated syndrome, while immunoglobulin M oligoclonal bands and CD62L levels may aid in risk stratification for progressive multifocal leukoencephalopathy in patients treated with natalizumab.[84,86]

2.5.3.3. Molecular biomarkers. Advances in molecular biology techniques have facilitated the identification of potential molecular biomarkers in MS. Translocator protein expressed in the outer mitochondrial membrane has been explored as a target for positron emission tomography (PET) imaging to visualize neuroinflammation.[82] Additionally, the mammalian target of rapamycin (mTOR) signaling pathway has been implicated in various processes relevant to MS pathogenesis, including autophagy, inflammasome activation, immune responses, and neurodegeneration.[80] Modulation of the mTOR pathway has shown therapeutic potential in animal models and preliminary clinical studies, highlighting its prospective role as a biomarker and therapeutic target. Tables 1 and 2 summarize the aforementioned models, recent pathogenic findings, and certain biomarkers of NDs.

3. Advances in the clinical treatment of NDs

3.1. Biological therapies

Cell therapy has shown significant therapeutic promise in treating NDs by replacing lost neurons and supporting neural repair. Clinical trials have primarily involved mesenchymal stem cells (MSCs) and bone marrow-derived stem cells, administered via intravenous or putamen injections. These trials have reported improvements in neural and motor functions, with good safety profiles over follow-up periods ranging from 3 months to 5 years.[93–95]

Recent advancements have focused on overcoming challenges, including extensive cell loss, limited neural cell regeneration capacity, and the presence of growth-inhibiting molecules, such as those released by astroglial scars, in chronic cases of spinal cord injury. Studies have highlighted the potential of MSCs in promoting

Table 1
Experimental models of neurodegenerative diseases.

Disease	Model	
Alzheimer's disease (AD)		
	Amyloid precursor protein (APP)/presenilin 1 (PS1) double transgenic mouse	57
	Five familial AD transgenes (5xFAD) mouse	
Parkinson's disease (PD)		
	6-Hydroxydopamine (6-OHDA) model	40–51
	MPTP model	
	Genetic models	
	Non-human primate models	
Amyotrophic lateral sclerosis (ALS)		
	Tar-DNA binding protein of 43 (TDP-43) and superoxide dismutase 1 (SOD1) models	52
	Metabolic dysfunction	
	Endoplasmic reticulum stress	
	Genetic animal models	
Multiple sclerosis (MS)		
	Experimental autoimmune encephalomyelitis (EAE)	74–76,78
	Cuprizone model	

Table 2
Recent pathogenic findings and biomarkers of neurodegenerative diseases.

Disease	Cellular Mechanisms	Biomarkers	
Alzheimer's disease (AD)			
	Dysfunction of microglia	Phosphorylated tau protein	
	Autophagy dysfunction	Brain amyloid and reactive astrocytes' blood biomarkers	
		Phospholipid and sphingolipid	
		Plasma aβ42/40 ratio and phosphorylated tau protein	
		Neurofilament light chain protein and glial fibrillary acidic protein	
Parkinson's disease (PD)			
	Oxidative stress	α-Synuclein	48,50
	Mitochondrial dysfunction	Neurofilament light chain (NFL)	
	Protein aggregation	DOPA decarboxylase (DDC)	
	Endoplasmic reticulum (er) stress	Leucine-rich repeat kinase 2(LRRK2) kinase activity	
	Neuroinflammation	Metabolite-based biomarkers	
	Genetic factors		
	α-Synuclein (SNCA)		
	LRRK2		
	PTEN induced kinase 1(PINK1) and parkin		
	Protein DJ-1(*DJ-1*)		
	vacuolar protein sorting 35(VPS35)		
	Mitochondrial function		
	Protein degradation		
	Immune response		
	Metabolic dysregulation		
Amyotrophic lateral sclerosis (ALS)			
	TDP-43 pathology	Proteomic approaches	52,56,57
	Nucleocytoplasmic transport deficits	MicroRNAs	
	Oxidative stress and DNA damage	Antioxidant biomarkers	
	Protein disulfide isomerase (PDI) activity	Blood biomarkers	
	Amyloid precursor protein (APP) interaction	Genetic biomarkers	
Multiple sclerosis (MS)			
	Oligodendrocyte and myelinating	Imaging biomarkers	
	Immune cell and neuroinflammation	Body fluid biomarkers	72,73
		Molecular biomarkers	

nerve cell regeneration and restoring motor and sensory functions in both humans and animals.[93] Additionally, the integration of nanotechnology with stem cell engineering has led to the emergence of stem cell nanotechnology, which has shown potential in drug delivery systems for the treatment of cancer and neurodegenerative, muscle, and blood diseases.[94]

Antisense oligonucleotides (ASOs) represent a novel therapeutic platform for targeting specific RNA sequences to modulate gene expression. Nusinersen, an ASO, has been approved for spinal muscular atrophy and has shown potential in treating ALS, HD, and AD.[96–98]

Recent studies have explored the use of ASOs for the targeting of natural antisense transcripts involved in various biological processes. The advantages of such therapies include targeted delivery and the ability to modify disease progression. For instance, ASOs targeting miR-10b have shown promise in preventing metastasis and stopping the growth of pre-existing metastases in triple-negative breast cancer models.[99] Additionally, ASOs are being investigated for their potential to treat NDs by reducing mutant protein levels, inhibiting mRNA translation, or altering pre-mRNA splicing.[97]

With the capability to differentiate into any cell type, iPSCs are a valuable tool for disease modeling and drug discovery. They provide a platform for “clinical trials in a dish”, allowing for the testing of therapeutic compounds on patient-specific cells. This approach can be utilized to identify potential treatments and understand disease mechanisms.[98,99]

Recent advancements in iPSC technology have focused on generating three-dimensional organoid models that replicate complex tissue structures in vitro. Such models are particularly useful for studying NDs and neuromotor disorders. Additionally, iPSCs have shown promising outcomes in regenerative therapies, as evidenced by their successful application in animal models and clinical trials for PD. Furthermore, iPSCs are being used to develop personalized disease models, which can help mitigate tumorigenic risks and other hurdles associated with stem cell therapies.[100]

3.2. Chemical drug therapies and conventional pharmacological approaches

Acetylcholinesterase Inhibitors: Drugs that enhance cholinergic neurotransmission, including donepezil, rivastigmine, and galantamine, are approved for symptomatic treatment of AD. These drugs work by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine, thereby increasing the levels of this neurotransmitter in the brain. This approach has shown to improve cognitive function and delay the progression of symptoms in AD patients.[101,102]

Monoamine Oxidase (MAO) Inhibitors: Compounds such as rasagiline and selegiline are used in PD to inhibit the breakdown of dopamine, thereby increasing its availability in the brain. These inhibitors have shown efficacy in reducing motor symptoms and improving the quality of life for PD patients. Safinamide, a newer MAO-B inhibitor, also impacts glutamatergic pathways, offering additional benefits in managing non-motor symptoms.[103–105]

Anti-Amyloid Therapies: Investigational drugs, such as aducanumab and lecanemab, aim to clear Aβ plaques, a hallmark of AD pathology. These therapies have shown promise in reducing the amyloid load in the brain and slowing disease progression, although their impact on cognitive outcomes has been mixed. Recent trials demonstrated that these drugs can slow clinical disease progression, marking a significant advancement in AD treatment.[106–108]

While these drugs provide symptomatic relief, their ability to modify the underlying disease progression remains limited. The search for more effective disease-modifying therapies continues,

with ongoing research into the molecular mechanisms of neurodegeneration.

Natural Products: The potential neuroprotective effects of traditional medicines, particularly from plant sources, have garnered significant interest. Compounds such as curcumin, resveratrol, and various alkaloids have shown promise in preclinical studies, exhibiting antioxidant, anti-inflammatory, and anti-amyloid properties. These natural products are being explored for their ability to modulate multiple pathways involved in neurodegeneration, offering a holistic approach to treatment.[109,110]

Drug Repurposing: Repurposing of existing drugs approved for other indications offers a faster and more cost-effective approach to drug development. For instance, the anti-leprosy drug clofazimine has been identified as a potential therapy for polyglutamine diseases (e.g., HD) through its activation of the peroxisome proliferator-activated receptor (PPAR)γ pathway. This strategy leverages the known safety profiles of existing drugs, accelerating the transition from bench to bedside.[102]

Stem Cell and Neurotrophic Factor Combinations: Combining stem cell transplantation with neurotrophic factors, such as BDNF and glial cell-derived neurotrophic factor, may enhance neuronal survival and differentiation. This approach aims to not only replace lost neurons, but also create a supportive environment for their growth and integration into existing neural networks.[109] As PD is pathologically characterized by loss of specific dopaminergic neurons in middle brain of the patients, transplantation of stem cells such as fetal brain derived neural stem cells (NSCs) and induced pluripotent stem cell-derived dopaminergic precursor cells has been shown to be effective for treatment of PD in animal models and clinical trials.[110]

Multi-Target Directed Ligands (MTDLs): MTDLs are designed to modulate multiple targets simultaneously, such as MAO inhibition combined with acetylcholinesterase inhibition or antioxidant properties. This strategy aims to address the complex pathophysiology of NDs by targeting several pathways involved in disease progression.[102]

Drug repurposing, or finding new therapeutic applications for existing drugs, has emerged as a promising strategy for NDs. This approach can accelerate drug development and reduce costs compared with traditional drug discovery pipelines.

Kinase Inhibitors: Originally developed for cancer treatment, certain kinase inhibitors have demonstrated neuroprotective effects in NDs. These drugs can modulate signaling pathways involved in cell survival and inflammation, offering potential benefits for conditions such as AD and PD.[102]

Clofazimine: As mentioned above, the anti-leprosy drug clofazimine has shown potential for treating polyglutamine diseases through its activation of the PPARγ pathway. This repurposing approach leverages the drug's known mechanisms of action to target new disease pathways.[102]

Nanotechnology offers innovative solutions to overcome the challenges of delivering therapeutic agents across the blood−brain barrier (BBB). Nanoparticle-based delivery systems can improve the solubility, stability, and targeted delivery of drugs to the brain. Amphiphilic nanocarriers, such as cubosomes, hexosomes, and liposomes, can be utilized to encapsulate hydrophobic compounds (e.g., curcumin), enhancing their bioavailability and brain delivery. These carriers also protect the drug from degradation and facilitate its transport across the BBB.[110] Nanoparticles can be functionalized with ligands or antibodies to facilitate their transport across the BBB or to target specific cell types in the brain. This targeted approach can increase the efficacy of the drug while minimizing off-target effects.[110] Additionally, nanoparticles can be used to deliver therapeutic genes or stem cells to the brain, potentially enabling regenerative approaches for NDs. This technology enhances the precision and efficiency of gene and cell therapies, offering new avenues for treatment.[110]

4. Clinical trials

Table 3 summarizes clinical trials of new drugs for NDs, obtained by searching the official websites of the China Center for Drug Evaluation and the U.S. Food and Drug Administration.

5. Conclusions and future directions

Recent advancements in understanding the pathogenesis of these NDs have highlighted their multifactorial nature, involving genetic mutations, environmental factors, neuroinflammation, oxidative stress, mitochondrial dysfunction, and protein aggregation.

In this review, we summarized the latest research on the pathogenesis and neurorestorative mechanisms of NDs. Key findings include the role of neuroinflammation driven by microglia and astrocytes, the impact of genetic mutations, such as *APOE* in AD and *LRRK2* in PD, and the importance of autophagy and mitochondrial quality control in maintaining neuronal health. Additionally, the development of animal models and the identification of blood biomarkers have provided valuable tools for studying disease mechanisms and evaluating potential therapies.

Neurorestorative strategies involving neuromodulation, immunomodulation, neurogenesis, axonal regeneration, and neuroplasticity, offer promising avenues for therapeutic intervention. These approaches aim to enhance the intrinsic repair mechanisms of the brain and improve functional outcomes for patients with NDs.

Future research should focus on developing therapies that modulate neuroinflammatory pathways. Elucidating the precise roles of microglia and astrocytes in different stages of NDs could lead to targeted interventions that mitigate chronic inflammation and promote neuroprotection. Continued exploration of the interplay among genetic predispositions and environmental exposures is crucial. Large-scale genomic studies and environmental risk assessments will help to identify new therapeutic targets and preventive strategies. Therapies aimed at enhancing autophagy and improving mitochondrial quality control hold potential for treating NDs. We need more research focused on identifying compounds that can safely and effectively modulate these pathways in humans. The continued development of precise animal models that closely mimic human NDs is essential for preclinical testing of new therapies. We anticipate that advances in gene editing technologies, such as CRISPR, will facilitate the creation of models that better represent the genetic and pathological features of NDs. Identification of reliable biomarkers for early diagnosis and monitoring of ND progression is also critical. Additional studies are needed to validate existing biomarkers, as well as to discover new biomarkers that can be used in clinical settings to improve patient outcomes. The integration of stem cell therapy, ASOs, and iPSCs into clinical practice offers promising avenues for treating NDs, ideally with further research focused on optimizing their safety and efficacy. Given the multifactorial nature of NDs, combination therapies that target multiple pathways simultaneously may offer the best chance for effective treatment. Additionally, we need further exploration of the synergistic effects of combining different therapeutic strategies. Advances in nanotechnology could improve the delivery of therapeutic agents across the BBB. Nanoparticle-based delivery systems that enhance the solubility, stability, and targeted delivery of drugs to the brain represent a promising area of research. Innovative clinical trial designs that incorporate biomarkers, advanced imaging techniques, and patient stratification based on genetic and molecular profiles are expected to accelerate the development of

Table 3
Clinical trials of newly developed drugs for neurodegenerative diseases.

Clinical Trials (drugs)		
Lecanemab	Phase 3 clinical trial	The clarity AD trial was a global, placebo-controlled, double-blind, parallel-group, randomized study involving 1,795 participants with early Alzheimer's disease (AD), including mild cognitive impairment (MCI) due to AD or mild AD dementia.
	Primary endpoint	Change from baseline in the clinical dementia rating-sum of boxes (CDR-SB) score at 18 months.
	Results	Lecanemab slowed the decline in CDR-SB scores by 27% compared to placebo, with a treatment difference of −0.45 ($p = 0.00005$). All key secondary endpoints, including reductions in amyloid plaque burden and improvements in cognitive and functional scales (ADAS-Cog14, ADCOMS, ADCS MCI-ADL), were also met with statistically significant results.
	Approval	Lecanemab has received traditional approval from the US FDA. Clinical registration number (NCT03887455).
Donanemab	Phase 3 clinical trial	The TRAILBLAZER-ALZ 2 trial was a randomized, double-blind, placebo-controlled study involving 1736 participants with early symptomatic AD, including MCI and mild dementia stages.
	Primary endpoint	Integrated Alzheimer's disease rating scale (iADRS) score at 76 weeks.
	Results	Donanemab reduced the risk of disease progression by 35% in early AD patients with low/medium tau levels and by 22% in the overall population. The treatment slowed cognitive and functional decline, with significant improvements in CDR-SB scores and other secondary endpoints.
	Approval	Donanemab is under regulatory review, with FDA action expected by early 2024. Clinical registration number (NCT04437511).
Remternetug	Phase 3 clinical trial	The TRAILRUNNER-ALZ 1 trial is a randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of remternetug in participants with early symptomatic AD.
	Primary endpoint	Percentage of participants who reach amyloid plaque clearance on amyloid PET scan at 52 weeks.
	Design	The study involves 600 participants in the double-blind treatment period, with an additional 640 participants in an open-label safety cohort. Participants receive remternetug or placebo via subcutaneous injection or intravenous infusion.
	Interim results	Phase 1 data showed significant amyloid plaque reduction, with 75% of participants achieving amyloid clearance at doses ranging from 700 to 2800 mg IV. Clinical registration number (NCT05463731).
Valiltramiprosate (ALZ-801)	Phase 3 clinical trial Mechanism	The APOLLOE4 trial targets early AD patients with the *APOE4* gene. Valiltramiprosate is a β-amyloid protein 42 inhibitor designed to reduce amyloid plaque formation and slow disease progression. Clinical registration number (NCT04770220).
Tavapadon	Phase 3 clinical trial	Four trials (TEMPO-1, TEMPO-2, TEMPO-3, and TEMPO-4) are evaluating the efficacy of tavapadon, an oral drug targeting dopamine D1 and D5 receptors, in early Parkinson's disease (PD) and as an adjunctive therapy for motor fluctuations. Clinical registration number (NCT04542499).
Prasinezumab	Phase IIb clinical trial	This trial is investigating the potential of prasinezumab, an α-synuclein-targeting antibody, in early PD patients. Clinical registration number (NCT03100149).
Other promising drugs		Anle138b, BIIB054, NPT088, PD01A, RO7046015: Various drugs targeting α-synuclein aggregation, supported by the Michael J. Fox foundation.
	RJK002 (NCT06493279)	An AAV gene therapy showing significant neuroprotective effects in preclinical ALS models, approved for clinical trials by China's CDE.
	Tofersen (NCT02623699)	An antisense oligonucleotide targeting *SOD1* gene mutations, actively under development
	Ibudilast (MN-166) (NCT04057898)	A phase 2b/3 trial investigating its neuroprotective effects in ALS patients, showing promise in slowing disease progression.
	Pridopidine (NCT04556656), CNM-Au8 (NCT05281484), RAPA-501 (NCT04220190)	Various drugs funded by the NIH under the ACT for ALS Act, targeting different mechanisms to treat ALS.

effective treatments. Adaptive trial designs and real-world evidence can also enhance the evaluation of new therapies.

In summary, despite significant progress in understanding the pathogenesis of NDs and the emergence of potential therapeutic approaches, patients with these diseases continue to face multiple challenges that make the development of effective treatments extremely complex. AD, PD, ALS, and HD are characterized by multifactorial etiologies, including genetic mutations, environmental factors, neuroinflammation, oxidative stress, mitochondrial dysfunction, and protein aggregation, making it difficult to simultaneously target the related pathways for treatment. Additionally, the lack of reliable biomarkers for early diagnosis, the insufficient precision of animal models, and the difficulty in delivering therapeutic drugs across the BBB further complicate treatment. Although some neuroprotective and neurorestorative therapies have shown promise, much more research and innovation are needed to explore the integrated regulation of multiple pathological mechanisms and the potential of combination therapies targeting multiple pathways. Future research should focus on the development of more precise animal models, optimization of nanoparticle-based drug delivery systems, and improvements in the safety and efficacy of stem cell therapies and ASOs. We anticipate that multidisciplinary efforts and continuous innovation will lead to more effective therapeutic strategies that ultimately improve the quality of life for patients with NDs.

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Authors' contribution

W.G., conceptualization, writing — original draft preparation, writing — review and editing, visualization, and supervision. L.C.,

project administration and funding acquisition. C.H., conceptualization. H.S., H.S.S., and F.H., validation. S.J., resources. All authors have read and agreed to the published version of the manuscript.

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