

Pharmacological Management of Neurodegenerative Disorders: Current and Future Approaches

Mukund Pache*, Hrutuja Kedar, Snehal Kond, Pratik Jadhav, Tejashree R. Kedar

Department of Pharmacology, K. V. N. Naik S. P. Sanstha's, Institute of Pharmaceutical Education & Research, Canada Corner, Nashik, 422002, Maharashtra, India

ABSTRACT

Neurodegenerative disorders (NDs) encompass a range of debilitating conditions characterised by progressive neuronal damage, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). These disorders significantly impact the quality of life of affected individuals, placing a considerable burden on healthcare systems globally. Despite substantial research, pharmacological treatment remains limited, primarily focusing on symptom management rather than halting or reversing disease progression. This review aims to explore the current state of the pharmacological management of NDs, highlighting established therapies and emerging treatment strategies. This article examines current drug treatments, their mechanisms of action, limitations, and ongoing advancements in therapeutic approaches. Disease-modifying therapies, innovative drug delivery systems aimed at overcoming the blood-brain barrier, repurposing existing drugs, and the role of personalised medicine have been explored. A particular emphasis is placed on promising agents such as monoclonal antibodies targeting amyloid-beta in AD, gene therapies in HD and ALS, and neuroprotective strategies. Additionally, challenges in neurodegenerative drug development, such as heterogeneity in patient responses and the complexity of trial designs, are discussed. Future directions, including the integration of artificial intelligence in drug discovery, multitarget approaches, and the importance of environmental and lifestyle interventions, are proposed as potential solutions to these challenges. This review provides an in-depth understanding of the current landscape of pharmacological therapies for NDs and sheds light on future avenues for more effective treatment strategies.

Keywords: Neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, pharmacological management

INTRODUCTION

Neurodegenerative disorders represent a group of chronic, progressive conditions characterised by irreversible damage to and dysfunction of neurons. These disorders are characterised by the gradual degeneration of specific neuronal populations, leading to cognitive, motor, and/or behavioural impairments¹. The most prevalent and well-studied neurodegenerative diseases include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, although other conditions, such as frontotemporal dementia and multiple system atrophy, also fall under this category. The exact causes of these disorders remain poorly understood, but they are commonly associated with abnormal protein aggregation, genetic mutations, and

mitochondrial dysfunction, among other pathological mechanisms². The global prevalence of neurodegenerative disorders is increasing due to the ageing population, making them a growing public health concern. Alzheimer's disease, for example, is the most common form of dementia, affecting an estimated 50 million people worldwide. Parkinson's disease affects approximately 10 million people, whereas Huntington's disease and ALS impact smaller but still significant portions of the population³. The societal burden of these diseases is immense, not only because of the healthcare costs associated with their management but also because of the emotional and social toll on patients, families, and caregivers. As neurodegenerative diseases progress,

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individuals typically lose the ability to perform everyday tasks, and their dependence on others for basic care increases, significantly reducing their quality of life⁴. Despite extensive research efforts, the pharmacological management of neurodegenerative disorders remains limited, with a primary focus on symptom management rather than modifying disease progression. Current treatments for AD, PD, HD, and ALS are often insufficient and provide only modest improvements in symptom control⁵. The lack of effective, disease-modifying therapies remains one of the major challenges in neurodegenerative medicine. For example, in Alzheimer's disease, acetylcholinesterase inhibitors and NMDA receptor antagonists offer only symptomatic relief and do not slow disease progression. Similarly, Parkinson's disease treatments, such as levodopa, can alleviate

motor symptoms but fail to address the underlying neurodegenerative process

1. Pathophysiology of Neurodegenerative Disorders

Neurodegenerative disorders share common pathogenic mechanisms that drive the progressive degeneration of neurons, although each condition also presents distinct pathophysiological features. These diseases are characterised primarily by accumulating misfolded proteins, oxidative stress, neuroinflammation, and mitochondrial dysfunction, impairing cellular processes and leading to neuronal death. Elucidating these shared mechanisms is crucial for identifying potential pharmacological targets^{6,7}.

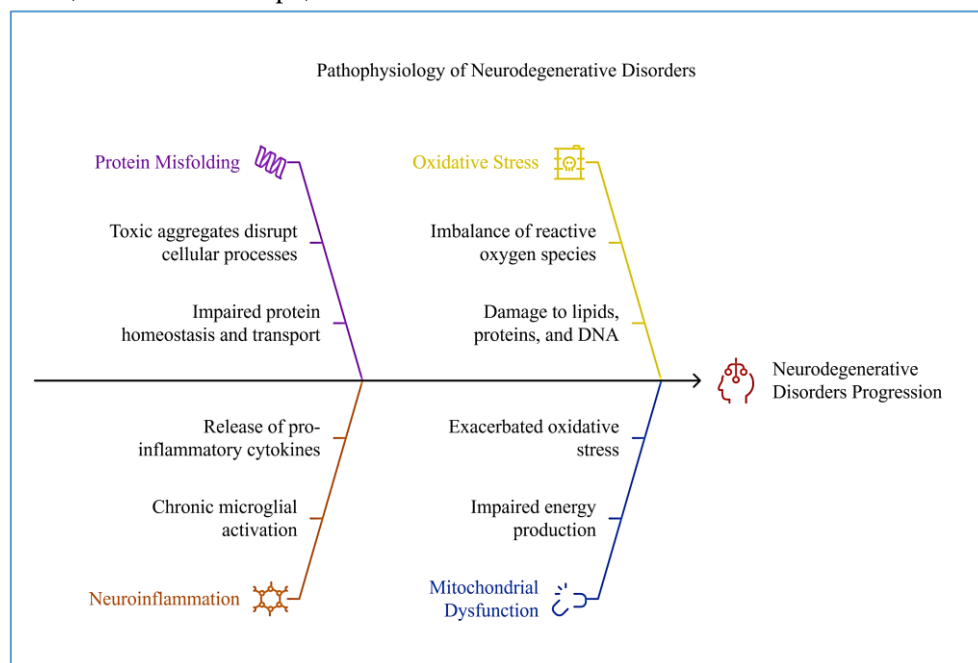


Figure 1 Pathophysiology and common mechanisms across neurodegenerative disorders

1.1. Common Mechanisms across Neurodegenerative Disorders

Protein Misfolding and Aggregation: A hallmark of many neurodegenerative diseases is the accumulation of misfolded proteins, which form toxic aggregates in the brain. These aggregates disrupt normal cellular processes, including protein homeostasis, axonal transport, and synaptic function⁸. For example, in Alzheimer's disease, amyloid-beta plaques and tau tangles are the main culprits, whereas in Parkinson's disease, alpha-synuclein forms Lewy bodies. In Huntington's disease, mutant Huntingtin proteins

aggregate, and in ALS, abnormal protein inclusions of TAR DNA-binding protein (TDP-43) and SOD1 are common features. These protein aggregates interfere with cellular functions and trigger neurotoxic pathways, contributing to neuronal death⁹.

Neuroinflammation: In many neurodegenerative diseases, an inflammatory response involving microglia and astrocytes is pivotal in disease progression. Neuroinflammation is characterised by the activation of microglia, the resident immune cells of the brain, which attempt to clear damaged neurons and protein aggregates. However, chronic microglial

activation results in the release of proinflammatory cytokines, which exacerbate neuronal damage and worsen the disease. This process is particularly evident in Alzheimer's disease and Parkinson's disease, where persistent neuroinflammation contributes to neurodegeneration^{10,11}.

Oxidative stress: Neurons are highly vulnerable to oxidative harm because of their elevated metabolic activity and abundance of polyunsaturated fatty acids. In neurodegenerative disorders, an imbalance between reactive oxygen species production and antioxidant defences in the brain results in oxidative stress. ROS can damage lipids, proteins, and DNA, impairing cellular function and leading to neuronal death¹². For example, in Parkinson's disease, the loss of dopaminergic neurons is partly ascribed to

oxidative stress, as dopamine can undergo auto-oxidation to generate ROS. Mitochondrial dysfunction, a central driver of oxidative stress, is also a hallmark of most neurodegenerative disorders⁶.

Mitochondrial Dysfunction: Mitochondrial dysfunction is closely linked to neurodegenerative disorders. In Parkinson's disease, damage to mitochondrial complexes, particularly in dopaminergic neurons, leads to impaired energy production and increased oxidative stress¹³. Similarly, in Alzheimer's disease, mitochondrial abnormalities impair synaptic function and contribute to the accumulation of amyloid-beta and tau proteins. This mitochondrial dysfunction exacerbates the cascade of events leading to neuronal death, making it a critical therapeutic target¹⁴.

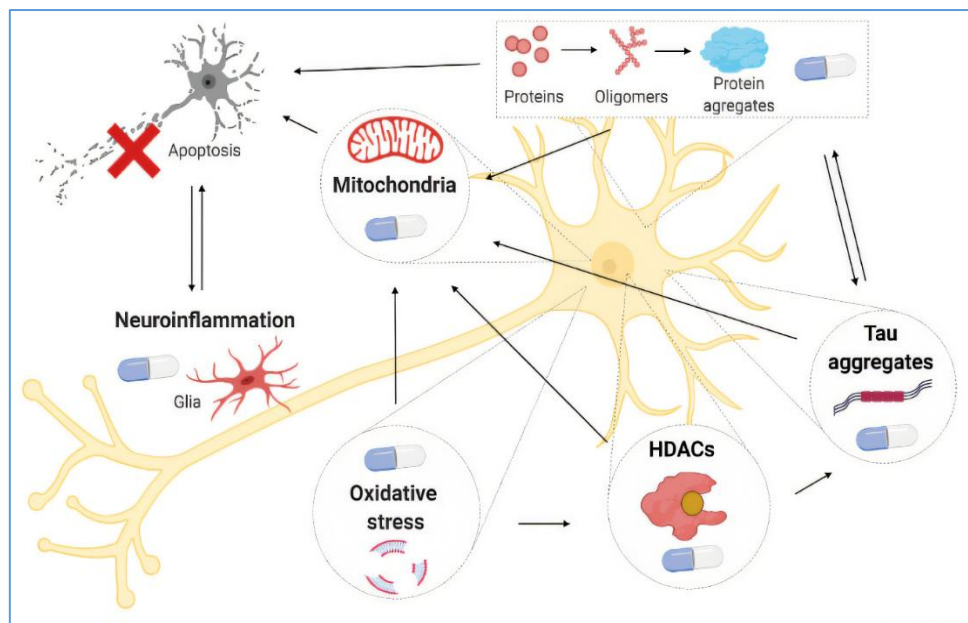


Figure 2 Molecular Targets for Pharmacological Intervention in Neurodegenerative Diseases

1.2. Disorder-specific Pathways

Alzheimer's disease (AD): Alzheimer's disease is characterised by the accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau proteins. These aggregations disrupt synaptic activity, whereas tau tangles destabilise microtubules and impair their intracellular transport¹⁵. Additionally, amyloid-beta plaques promote neuroinflammation, further exacerbating the disease process. The loss of cholinergic neurons is central to the cognitive decline observed in Alzheimer's disease, which is why

acetylcholinesterase inhibitors are commonly used to provide symptomatic relief¹⁶.

Parkinson's disease (PD): Parkinson's disease is characterised by the degeneration of dopaminergic neurons in the substantia nigra, a brain region critical for motor control. The hallmark pathological feature is the accumulation of alpha-synuclein protein in Lewy bodies, which disrupts synaptic vesicle release and impairs dopaminergic signalling. This dopamine deficiency results in the characteristic motor symptoms of PD, including tremors, rigidity, and bradykinesia. Oxidative stress and mitochondrial dysfunction are central to the pathogenesis of PD and

contribute to the progressive loss of dopaminergic neurons^{17,18}.

Huntington's disease (HD): HD is caused by a mutation in the HTT gene, which encodes the huntingtin protein. This mutation leads to an expanded polyglutamine repeat, forming toxic protein aggregates that disrupt neuronal function. The striatum is particularly vulnerable, as toxic proteins interfere with neurotransmitter release, axonal transport, and cellular signalling. The motor symptoms of Huntington's disease, including chorea, stem from the loss of neurons in the basal ganglia, a brain region crucial for motor control¹⁹.

Amyotrophic Lateral Sclerosis (ALS): ALS is a progressive neurodegenerative disorder that primarily affects motor neurons, leading to muscle weakness, atrophy, and paralysis. The disease is associated with mutations in several genes, including SOD1, C9ORF72, and TDP-43, all of which contribute to protein aggregation and neuroinflammation. SOD1 mutations impair the antioxidant defence system, resulting in oxidative stress²⁰. Additionally, TDP-43 aggregation disrupts RNA processing and axonal transport, further exacerbating motor neuron degeneration. The impact of ALS on both upper and lower motor neurons distinguishes it from other neurodegenerative conditions²¹.

1.3. Implications for Drug Targets

Understanding the common and disorder-specific pathological mechanisms underlying neurodegenerative disorders has paved the way for identifying potential drug targets. For example, therapies targeting protein misfolding have become a central focus of research. Neuroprotective agents aimed at reducing oxidative stress and improving mitochondrial function hold promise for treating Parkinson's disease and amyotrophic lateral sclerosis. Additionally, immunotherapies and gene therapies targeting specific mutations or pathways have shown potential in preclinical and early clinical studies^{22,23}. In summary, the pathophysiology of neurodegenerative disorders is complex and involves protein misfolding, neuroinflammation, oxidative stress, and mitochondrial dysfunction. A better comprehension of these processes is crucial for developing effective pharmacological therapies that

can modify disease progression and improve patient outcomes.

2. Current pharmacological approaches

The pharmacological management of neurodegenerative disorders primarily focuses on alleviating symptoms, slowing disease progression, and improving quality of life, as there are no definitive cures for these conditions. This section reviews the currently approved therapies for Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, along with their mechanisms of action. Additionally, the limitations of these therapies are discussed^{24,25}.

2.1. Approved Therapies

Alzheimer's Disease (AD): Acetylcholinesterase inhibitors are the mainstay of symptomatic treatment for Alzheimer's disease. These drugs work by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine, a neurotransmitter essential for memory and cognitive function^{26,27}. By increasing acetylcholine levels in the brain, these inhibitors help mitigate cognitive decline. Donepezil, the most commonly prescribed acetylcholinesterase inhibitor, has shown moderate benefits in improving cognitive function and slowing disease progression, although the effects are typically modest and transient. Rivastigmine and galantamine also provide similar benefits²⁸. Memantine is an N-methyl-D-aspartate receptor antagonist that helps regulate glutamate activity. Excessive glutamate signalling is thought to contribute to neuronal damage and cell death, particularly in Alzheimer's disease²⁹. Memantine works by blocking NMDA receptors, which are involved in excitotoxicity, thereby protecting neurons from overstimulation. Memantine is often used in moderate-to-severe stages of Alzheimer's disease, either as a monotherapy or in combination with acetylcholinesterase inhibitors, and has been shown to provide modest improvements in cognitive and functional symptoms³⁰.

Parkinson's Disease (PD): Dopaminergic agents are the mainstays of Parkinson's disease treatment. Levodopa remains the most effective and widely used option. L-DOPA is converted into dopamine in the brain, compensating for the loss of dopaminergic neurons in the substantia nigra. This alleviates motor

symptoms such as rigidity, bradykinesia, and tremors. However, long-term levodopa use is associated with motor fluctuations and the development of dyskinesias^{31,32}. To enhance its effects, levodopa is often combined with carbidopa, which prevents the peripheral conversion of L-DOPA into dopamine, thereby reducing side effects such as nausea³³. Dopamine agonists, such as pramipexole and ropinirole, can be used as monotherapies for early Parkinson's disease or as adjuncts to levodopa in later stages. These agents directly stimulate dopamine receptors, mimicking the action of dopamine. Compared with levodopa, dopamine agonists tend to have fewer motor fluctuations, but they can cause side effects such as compulsive behaviours and somnolence³⁴. Monoamine oxidase B inhibitors, including rasagiline and selegiline, prevent the breakdown of dopamine by blocking the MAO-B enzyme. This increases dopamine availability in the brain³⁵. MAO-B inhibitors have demonstrated neuroprotective effects and are used to treat Parkinson's motor symptoms, especially in the early stages. They are often combined with levodopa to enhance their effects and may help delay the need for higher levodopa doses³⁶.

Huntington's Disease (HD): Tetrabenazine, a vesicular monoamine transporter 2 inhibitor, is used to treat characteristic involuntary jerking movements, or chorea, associated with Huntington's disease¹⁹. By reducing the release of dopamine from presynaptic neurons, tetrabenazine decreases dopaminergic activity in the brain, which helps alleviate motor

symptoms. However, these drugs can cause side effects such as depression, sedation, and Parkinsonism, so they should be used cautiously in patients with a history of depression or mood disorders^{32,37}.

Antisense oligonucleotides (ASOs): Antisense oligonucleotides, although not yet approved for clinical use, have shown promise in preclinical and early clinical trials as potential disease-modifying treatments for Huntington's disease³⁸. ASOs are designed to bind to the mutant huntingtin gene, which causes the aggregation of toxic proteins in HD and reduces the expression of the mutant protein. By preventing the toxic effects of the mutant protein rather than just alleviating symptoms, ASOs represent a promising approach³⁹.

Amyotrophic Lateral Sclerosis (ALS): Riluzole, the first drug approved for ALS, has modest effects on extending survival. It is thought to work by inhibiting glutamate release and blocking postsynaptic glutamate receptors, thereby reducing excitotoxicity and neuronal damage. However, riluzole only slightly delays disease progression and does not significantly improve motor function⁴⁰. Edaravone, an antioxidant that scavenges reactive oxygen species, plays a key role in ALS pathophysiology. By reducing oxidative stress, edaravone can help protect motor neurons from damage and slow the progression of the disease. It has shown modest benefits in improving functional measures, such as the ALS functional rating scale, but it does not stop the disease entirely⁴¹.

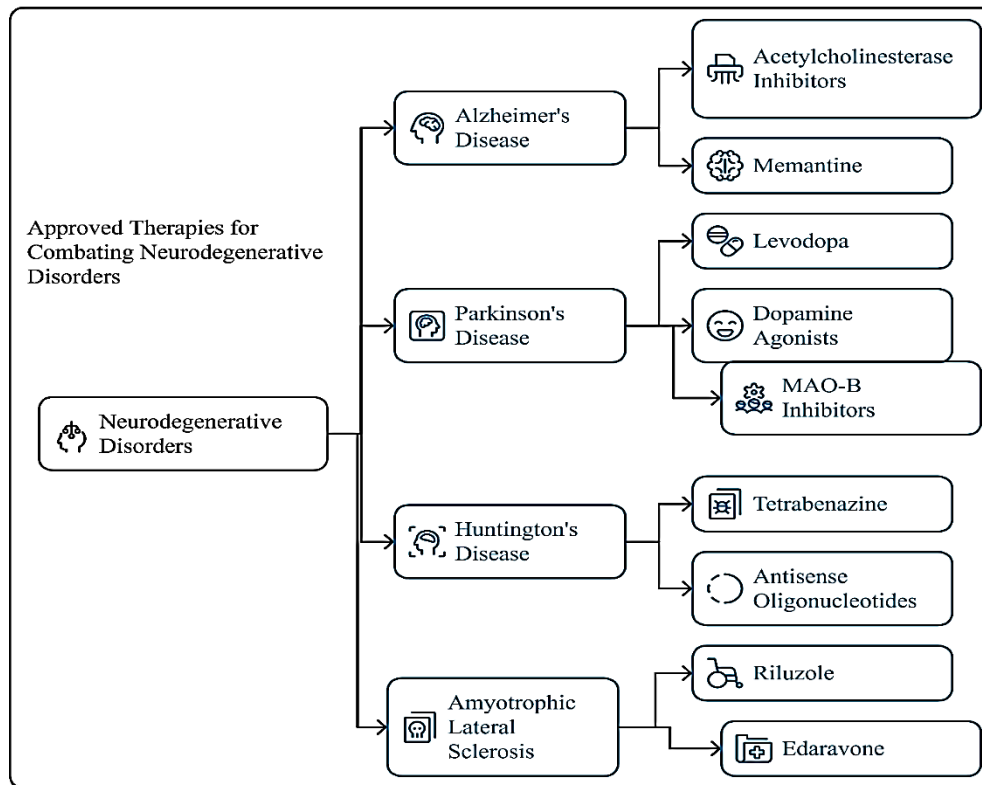


Figure 3 Approved therapies for the management of neurodegenerative disorders

2.2. Limitations of Current Therapies

Despite the availability of these therapies, several limitations persist in the pharmacological treatment of neurodegenerative diseases.

Lack of disease-modifying treatments: Although current therapies can alleviate symptoms and slow disease progression to some degree, they are unable to halt or reverse the underlying neurodegenerative processes^{42,43}. The primary aim of existing treatments is to manage symptoms, but patients continue to experience a decline in cognitive and motor function over time.

Limited efficacy and side effects: Although the most commonly prescribed medications, such as levodopa for Parkinson's disease and acetylcholinesterase inhibitors for Alzheimer's disease, can provide some symptomatic relief, their efficacy is often limited. Moreover, these drugs are frequently associated with side effects, including dyskinesias (involuntary movements) in PD patients treated with levodopa or gastrointestinal issues in those taking acetylcholinesterase inhibitors. Similarly, the use of tetrabenazine for Huntington's disease is limited by its

potential to cause psychiatric side effects such as depression and anxiety^{44,45}.

Challenges with blood-brain barrier (BBB) penetration: The blood-brain barrier poses a significant challenge in delivering many drugs, particularly those targeting neurodegenerative conditions. While some treatments, such as levodopa and memantine, can penetrate the BBB, others, including gene therapies and large-molecule drugs such as monoclonal antibodies, face substantial hurdles in reaching their intended targets within the brain^{46,47}. This issue has prompted research into innovative drug delivery systems, including nanoparticle-based carriers and intranasal administration techniques, to overcome this barrier. Current pharmacological treatments for neurodegenerative disorders can provide some symptomatic relief and moderate improvements, but they do not address the underlying causes of these diseases. Persistent issues with efficacy, side effects, and drug delivery pose significant barriers to developing more effective therapies. The next wave of drug development must focus on developing disease-modifying treatments that can halt or even

reverse disease progression. Overcoming challenges related to the blood-brain barrier and patient heterogeneity is also crucial for advancing more impactful treatments^{47,48}.

3. Emerging Pharmacological Approaches

Current pharmacological treatments for neurodegenerative diseases provide only symptomatic relief without addressing the underlying

causes or halting disease progression. This section explores emerging pharmacological approaches that hold promise for more effective, disease-modifying therapies. These include gene therapy, stem cell therapy, and novel drug classes that target the molecular pathways involved in neurodegeneration. Additionally, we discuss the progress of clinical trials and the challenges faced in bringing these therapies to market.

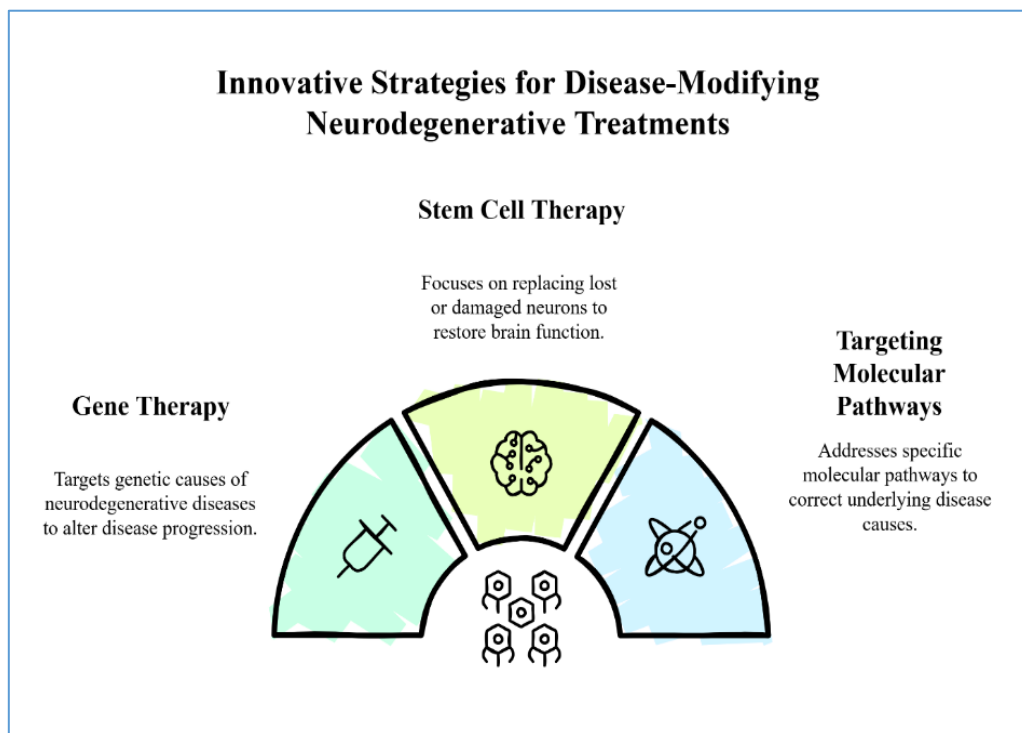


Figure 4 Emerging pharmacological approaches for treating neurodegenerative diseases

3.1. Gene therapy

Gene therapy offers significant promise as a disease-modifying treatment for neurodegenerative diseases. By directly targeting the genetic causes of these disorders, gene therapy has the potential to alter the course of the disease, slowing or halting neurodegeneration, and potentially providing a long-term solution^{49,50}. One of the key advantages of gene therapy is its ability to bypass the blood-brain barrier, which is a significant hurdle for many traditional small-molecule drugs.

Gene silencing for Huntington's disease (HD): Huntington's disease is caused primarily by a CAG repeat expansion in the huntingtin gene, leading to the production of a toxic protein that accumulates in neurons⁵¹. Gene silencing approaches, such as antisense oligonucleotides and RNA interference, aim

to reduce or eliminate the expression of the mutant huntingtin gene. These therapies target the messenger RNA produced by the faulty gene, thereby preventing the synthesis of the toxic protein⁵².

Several preclinical and early-phase clinical trials are exploring the potential of ASOs for Huntington's disease. Notably, the drug IONIS-HTTRx is an ASO designed to reduce the production of the mutant huntingtin protein. Early clinical trials have demonstrated promising results, with patients exhibiting reductions in mutant huntingtin protein levels and improvements in biomarkers of disease. However, larger studies are necessary to confirm these findings and assess the long-term efficacy and safety of this approach^{53,54}.

Gene therapy for amyotrophic lateral sclerosis (ALS): ALS is driven primarily by mutations in the

SOD1 gene, leading to the accumulation of misfolded proteins and the degeneration of motor neurons. Researchers have explored gene therapy approaches that target the SOD1 gene, aiming to silence the mutant gene and prevent its toxic effects⁵⁵. Tominersen, an ASO that targets SOD1, has shown potential in preclinical studies to reduce the accumulation of mutant proteins in motor neurons. Additionally, AAV-mediated gene delivery has been investigated as a method to deliver therapeutic genes directly into motor neurons to enhance neuroprotection. Early trials indicate that such strategies could slow the progression of ALS and potentially halt neuronal damage. However, challenges related to delivery methods, immune responses, and long-term effects remain to be addressed^{56,57}.

3.2. Stem Cell Therapy

Stem cell-based therapies have emerged as a potential solution for replacing lost or damaged neurons in neurodegenerative diseases. Using pluripotent stem cells, neural stem cells, or induced pluripotent stem cells, researchers have aimed to generate new, healthy neurons that can integrate into affected brain regions.

Stem cell therapy in Parkinson's disease (PD):

Parkinson's disease is characterised by the loss of dopaminergic neurons in the substantia nigra. Several studies have focused on the use of stem cells to replace these lost neurons, aiming to restore dopaminergic function and alleviate motor symptoms^{31,32}. Dopamine-producing neurons derived from human embryonic stem cells or iPSCs have shown promise in preclinical models of PD. These cells are transplanted into the striatum or substantia nigra, where they are expected to integrate into the existing neural network and restore dopamine signalling⁵⁸. Clinical trials using fetal-derived dopaminergic neurons have yielded mixed results. While some studies report modest improvements in motor function, others have been hindered by issues such as the development of dyskinesias or tumour growth⁵⁹. Recent advances in gene editing technologies, such as CRISPR-Cas9, have also been employed to increase the survival and function of transplanted stem cells, but safety concerns and the risk of off-target effects require careful evaluation⁶⁰.

Stem Cell Therapy in Alzheimer's Disease (AD):

The application of stem cells in Alzheimer's disease focuses on their potential to replace damaged neurons and restore cognitive function. Recent studies have investigated the transplantation of neural progenitor cells derived from human stem cells into animal models of AD⁶¹. These cells can differentiate into neurons and glial cells, potentially replacing lost or damaged cells in brain regions affected by AD, such as the hippocampus and cortex⁶². Clinical trials using stem cells for AD have faced significant challenges, particularly those related to the integration and survival of transplanted cells. Additionally, there are concerns about the ethical implications and long-term effects of using stem cells, especially if they are derived from embryonic sources. Advances in stem cell engineering, such as the development of patient-specific iPSCs, offer the potential to overcome some of these challenges by using autologous cells, thereby minimising immune rejection^{63,64}.

3.3. Targeting Molecular Pathways

In addition to gene and stem cell therapies, several emerging pharmacological approaches aim to address specific molecular pathways implicated in neurodegeneration. These approaches endeavour to correct or alleviate the underlying causes of neurodegenerative diseases by targeting dysregulated proteins, cellular pathways, or metabolic processes.

1) Targeting Misfolded Proteins

Protein misfolding and aggregation are central pathological hallmarks of numerous neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. Consequently, therapeutic strategies aimed at preventing or reversing such protein aggregation are garnering increasing attention⁶⁵.

Alzheimer's Disease: The accumulation of amyloid-beta plaques and tau tangles is a well-established hallmark of Alzheimer's disease. Several monoclonal antibodies, such as aducanumab and lecanemab, have been designed to target these amyloid plaques and facilitate their clearance from the brain⁶⁶. While these therapies have demonstrated some success in reducing the amyloid burden, their impact on cognitive improvement has been mixed, leading to ongoing debates about their true efficacy.

Additionally, researchers are exploring tau-targeting therapies to prevent tau aggregation and mitigate its detrimental effects on neuronal function⁶⁷.

Parkinson's Disease: Parkinson's disease is characterised by the accumulation of misfolded alpha-synuclein protein, which is a key pathological feature of this disease. Several therapeutic strategies have been explored to target and reduce the accumulation of this aberrant protein⁶⁸. For example, prasinezumab, a monoclonal antibody that binds to alpha-synuclein, is currently undergoing clinical trials and has demonstrated some promise in alleviating motor symptoms in early-stage studies⁶⁹.

Huntington's Disease: Gene silencing approaches targeting mutant huntingtin are being explored as a means to reduce protein aggregation, as mentioned previously. Additionally, small molecules designed to disrupt the aggregation of toxic proteins are also under investigation as complementary therapeutic strategies⁷⁰.

2) Neuroinflammation Modulation

Neuroinflammation is a critical factor in the development of many neurodegenerative diseases. Chronic activation of the brain's immune system, driven primarily by microglia, contributes to neuronal damage and disease progression. As such, targeting neuroinflammation holds promise as a strategy for developing disease-modifying therapies.

Parkinson's Disease: Emerging evidence suggests that inhibiting the activation of microglia or modulating their response could reduce neuroinflammation and protect dopaminergic neurons in Parkinson's disease⁷¹. Specifically, P2X7 receptor antagonists and NLRP3 inflammasome inhibitors are being investigated as prospective therapeutic approaches for this condition⁷².

Alzheimer's Disease: Emerging evidence suggests that targeting neuroinflammation could be a promising approach for treating neurodegenerative conditions such as Alzheimer's disease. Anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs and the tetracycline antibiotic minocycline, are being explored as adjuncts to standard therapies⁷³. The aim is to reduce the chronic activation of the brain's immune system, driven

primarily by microglia, and mitigate the damaging effects of neuroinflammation on neurons.

3.4. Challenges in Emerging Therapies

Despite the promise of emerging therapies, several challenges remain before they can be widely implemented in clinical practice. These challenges include the following:

Delivery and Targeting: Overcoming the effective delivery of therapeutic agents, particularly for gene- and stem cell-based therapies, remains a significant challenge. Many essential treatments, such as gene-silencing drugs or biologics, must first cross the formidable blood-brain barrier to reach their target sites within the brain⁴⁷. However, new strategies, including nanoparticle-based drug delivery systems, are being developed to enhance the targeted delivery of these therapies⁷⁴.

Safety Concerns: Although gene therapy and stem cell-based approaches hold significant promise, they also raise safety concerns, such as the risk of immune reactions, tumour formation, and unintended effects. Rigorous preclinical and clinical testing is crucial for evaluating the safety profiles of these therapies before they can be approved for use⁷⁵.

Long-term efficacy: While early-phase trials of emerging therapies have yielded promising results, their long-term efficacy remains uncertain. In some instances, the therapeutic benefits may diminish over time, and the potential for adverse effects could increase with prolonged use. Consequently, longitudinal studies are essential to ascertain the true effectiveness and safety of these therapies⁷⁶.

Emerging pharmacological approaches, such as gene therapy, stem cell therapy, and molecular pathway modulation, hold promise for the treatment of neurodegenerative diseases. While many of these therapies remain in early-stage clinical trials, they have the potential to modify the disease course and offer more effective treatments than currently available options do. However, significant challenges concerning delivery, safety, and long-term efficacy must be addressed before these therapies can become part of routine clinical practice. Ongoing research and clinical trials will be crucial in shaping the future landscape of neurodegenerative disease treatment^{77,78}.

4. Combination Therapies and Future Directions

Given the multifactorial nature of neurodegenerative disorders (NDs), single-agent therapies often fail to adequately halt disease progression. Combination therapies, which target multiple pathological pathways simultaneously, are increasingly being explored to improve treatment outcomes.

4.1. Combination Therapies

Multi-Drug Regimens: Neurodegenerative diseases involve overlapping mechanisms such as protein aggregation, oxidative stress, and neuroinflammation. Combining agents that address these distinct pathways offers synergistic benefits⁷⁹. For example, combining acetylcholinesterase inhibitors with NMDA receptor antagonists has shown modest improvements in cognitive function in patients with Alzheimer's disease. Similarly, in Parkinson's disease, combining levodopa with dopamine agonists or MAO-B inhibitors can enhance dopaminergic signalling while reducing motor fluctuations⁸⁰.

Adjunctive use of neuroprotective agents: Antioxidants, anti-inflammatory agents, and mitochondrial enhancers are promising candidates for combination therapies. Agents such as edaravone and riluzole, which are already approved for ALS, could be used alongside other neurodegenerative treatments⁸¹.

Gene and Immunotherapy Combinations: Recent clinical trials are exploring the use of gene-silencing therapies alongside monoclonal antibodies to reduce toxic protein accumulation in conditions such as Huntington's disease and Alzheimer's disease. These combinations aim to both decrease the production of pathological proteins and increase their clearance from the brain⁸². According to recent reports, the development of multifunctional neuroprotective and neurorestorative drugs for disorders such as Parkinson's disease and Alzheimer's disease is a

growing area of research⁸³. These drugs are designed to simultaneously target multiple pathological pathways, offering more comprehensive and potentially disease-modifying treatment approaches.

4.2. Future Directions

Precision Medicine Approaches: Advances in genomics and biomarker research have enabled the development of personalised treatment regimens tailored to an individual's genetic profile, disease stage, and response to therapy^{84,85}. Future research should focus on stratifying patients for customised therapeutic interventions.

Artificial Intelligence in Drug Development: AI-driven platforms are revolutionising drug discovery by identifying novel therapeutic targets and predicting drug efficacy. Integrating AI with existing neurodegenerative research can accelerate the development of new combination therapies and optimise clinical trial designs⁸⁶⁻⁸⁸.

Advanced Drug Delivery Systems: The blood-brain barrier remains a major obstacle in neurodegenerative treatment. Future innovations in nanoparticle carriers, liposomal systems, and intranasal delivery methods hold promise for improving drug penetration into the brain^{89,90}.

Lifestyle and Environmental Interventions: In addition to pharmacological strategies, incorporating lifestyle modifications such as dietary changes, physical exercise, and cognitive training into combination regimens may offer additional neuroprotective benefits. Research into the gut-brain axis and its influence on neurodegeneration could lead to novel dietary interventions²⁹.

Regenerative Therapies: Stem cell transplantation and neurogenesis-promoting agents are being actively investigated. Future studies should focus on enhancing the survival, integration, and functional restoration of transplanted cells in damaged brain regions^{91,92}.

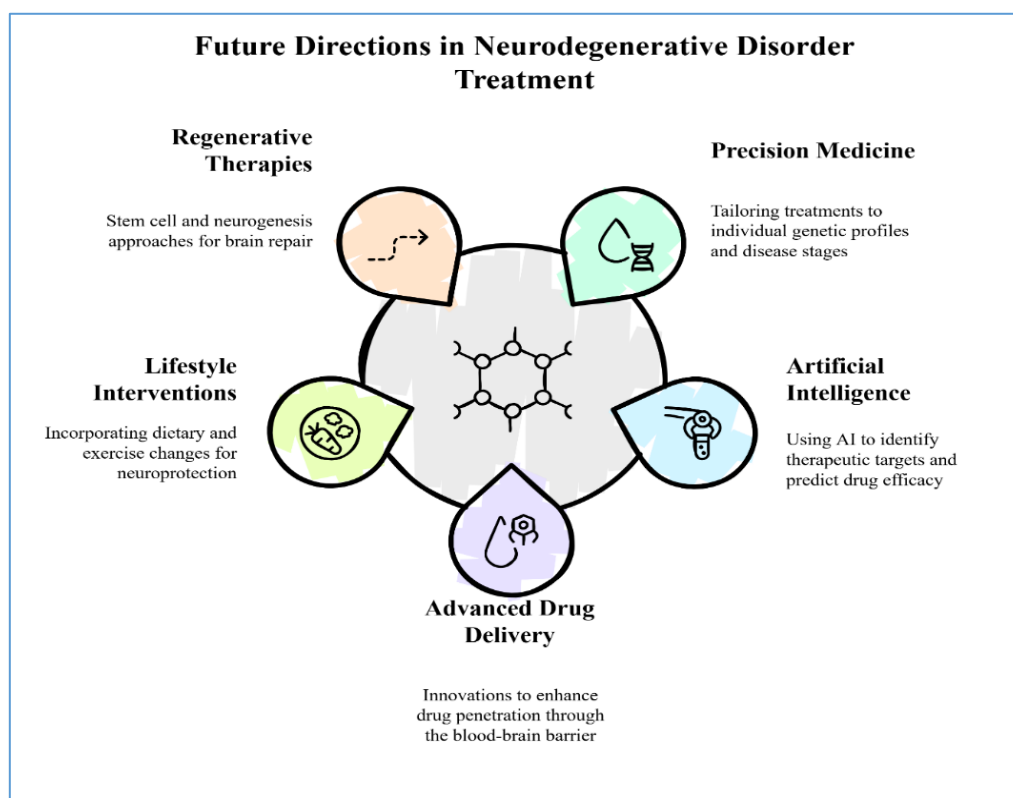


Figure 5 Future directions in neurodegenerative disease treatment

In conclusion, while current therapies offer symptomatic relief, the future lies in multitarget combination regimens, precision medicine, and innovative delivery systems. Collaborative efforts across disciplines are essential for translating these emerging strategies into effective treatments for neurodegenerative disorders.

CONCLUSION:

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are characterised by progressive neuronal loss and significant functional decline. Current pharmacological treatments primarily manage symptoms without halting disease progression, highlighting the urgent need for more effective therapies. Advances in gene therapy, monoclonal antibodies, and neuroprotective agents offer potential pathways toward disease modification, although challenges related to safety, long-term efficacy, and drug delivery remain significant. The future success of therapeutic approaches will likely depend on multitarget combination strategies addressing various disease mechanisms, including protein aggregation, neuroinflammation, and oxidative stress. Furthermore, the development of

personalised treatments and improved drug delivery systems could enhance therapeutic efficacy. The integration of artificial intelligence and emerging technologies will play a crucial role in accelerating drug discovery and optimising clinical strategies. Despite the limitations of current treatments, ongoing research and innovation provide hope for future breakthroughs that can slow or even reverse the progression of neurodegenerative diseases.

REFERENCE

1. Bloomingdale P, Karelina T, Ramakrishnan V, et al. Hallmarks of Neurodegenerative Disease: A Systems Pharmacology Perspective. *Nature Portfolio* 2022;11(11):1399–1429; doi: 10.1002/psp4.12852.
2. Li A, Tyson J, Patel SG, et al. Emerging Nanotechnology for Treatment of Alzheimer's and Parkinson's Disease. *Frontiers Media* 2021;9; doi: 10.3389/fbioe.2021.672594.
3. Chopade P, Chopade N, Zhao Z, et al. Alzheimer's and Parkinson's Disease Therapies in the Clinic. *Wiley* 2022;8(1); doi: 10.1002/btm2.10367.

4. Warren A. An Integrative Approach to Dementia Care. *Frontiers Media* 2023;4; doi: 10.3389/fragi.2023.1143408.
5. Lamptey RNL, Chaulagain B, Trivedi R, et al. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. *Multidisciplinary Digital Publishing Institute* 2022;23(3):1851–1851; doi: 10.3390/ijms23031851.
6. Riederer P, Nagatsu T, Youdim MBH, et al. Lewy Bodies, Iron, Inflammation and Neuromelanin: Pathological Aspects Underlying Parkinson's Disease. *Springer Science+Business Media* 2023;130(5):627–646; doi: 10.1007/s00702-023-02630-9.
7. Amartumur S, Nguyen HM, Huynh T, et al. Neuropathogenesis-on-chips for neurodegenerative diseases. *Nature Portfolio* 2024;15(1); doi: 10.1038/s41467-024-46554-8.
8. Dhapola R, Sarma P, Medhi B, et al. Recent Advances in Molecular Pathways and Therapeutic Implications Targeting Mitochondrial Dysfunction for Alzheimer's Disease. *Springer Science+Business Media* 2021;59(1):535–555; doi: 10.1007/s12035-021-02612-6.
9. Mead RJ, Shan N, Reiser HJ, et al. Amyotrophic Lateral Sclerosis: A Neurodegenerative Disorder Poised for Successful Therapeutic Translation. *Nature Portfolio* 2022;22(3):185–212; doi: 10.1038/s41573-022-00612-2.
10. Frost G, Jonas LA, Li Y-M. Friend, Foe or Both? Immune Activity in Alzheimer's Disease. *Frontiers Media* 2019;11; doi: 10.3389/fnagi.2019.00337.
11. Zhang W, Xiao D, Mao Q, et al. Role of Neuroinflammation in Neurodegeneration Development. *Springer Nature* 2023;8(1); doi: 10.1038/s41392-023-01486-5.
12. Seixas AF, Quendera AP, Sousa JPA, et al. Bacterial Response to Oxidative Stress and RNA Oxidation. *Frontiers Media* 2022;12; doi: 10.3389/fgene.2021.821535.
13. Alshial EE, Abdulghaney MI, Wadan A-HS, et al. Mitochondrial Dysfunction and Neurological Disorders: A Narrative Review and Treatment Overview. *Elsevier BV* 2023; 334:122257–122257; doi: 10.1016/j.lfs.2023.122257.
14. Chanchal Sharma 1 2 ,“Mitochondrial Dysfunction as a Driver of Cognitive Impairment in Alzheimer's Disease - PubMed.” Mar. 2021. Accessed: Jan. 07, 2025. Available: <https://pubmed.ncbi.nlm.nih.gov/34063708/>
15. Li H, Ye T, Liu X, et al. The role of signaling crosstalk of microglia in hippocampus on progression of ageing and Alzheimer's disease. *Elsevier BV* 2023;13(7):788–805; doi: 10.1016/j.jpha.2023.05.008.
16. Yang X. Applications of Nanotechnology in the Treatment of Alzheimers Disease. 2023;4(1):119–133; doi: 10.54254/2753-8818/4/20220532.
17. Chatzaki C, Skaramagkas V, Kefalopoulou Z, et al. Can Gait Features Help in Differentiating Parkinson's Disease Medication States and Severity Levels? A Machine Learning Approach. *Multidisciplinary Digital Publishing Institute* 2022;22(24):9937–9937; doi: 10.3390/s22249937.
18. Stykel MG, Ryan SD. Nitrosative Stress in Parkinson's Disease. *Nature Portfolio* 2022;8(1); doi: 10.1038/s41531-022-00370-3.
19. Wilton DK, Mastro K, Heller MD, et al. Microglia and complement mediate early corticostriatal synapse loss and cognitive dysfunction in Huntington's disease. *Nature Portfolio* 2023;29(11):2866–2884; doi: 10.1038/s41591-023-02566-3.
20. Morata-Tarifa C, Azkona G, Glass JD, et al. Looking backward to move forward: a meta-analysis of stem cell therapy in amyotrophic lateral sclerosis. *Nature Portfolio* 2021;6(1); doi: 10.1038/s41536-021-00131-5.
21. Rothstein JD. Current Hypotheses for the Underlying Biology of Amyotrophic Lateral Sclerosis. *Wiley* 2009;65(S1); doi: 10.1002/ana.21543.
22. Lindholm P, Saarma M. Cerebral Dopamine Neurotrophic Factor Protects and Repairs Dopamine Neurons by Novel Mechanism. *Springer Nature* 2021;27(3):1310–1321; doi: 10.1038/s41380-021-01394-6.
23. Gouda N, Elkamhawy A, Cho J. Emerging Therapeutic Strategies for Parkinson's Disease and Future Prospects: A 2021 Update. *Multidisciplinary Digital Publishing Institute*

- 2022;10(2):371–371; doi: 10.3390/biomedicines10020371.
24. Marsili L, Sharma J, Outeiro TF, et al. Stem Cell Therapies in Movement Disorders: Lessons from Clinical Trials. *Multidisciplinary Digital Publishing Institute* 2023;11(2):505–505; doi: 10.3390/biomedicines11020505.
25. Salman MM, Al-Obaidi Z, Kitchen P, et al. Advances in Applying Computer-Aided Drug Design for Neurodegenerative Diseases. *Multidisciplinary Digital Publishing Institute* 2021;22(9):4688–4688; doi: 10.3390/ijms22094688.
26. Muñoz-Núñez E, Quiroz-Carreño S, Pastene E, et al. Assessments of Ceanothanes Triterpenes as Cholinesterase Inhibitors: An Investigation of Potential Agents with Novel Inspiration for Drug Treatment of Neurodegenerative Diseases. *Multidisciplinary Digital Publishing Institute* 2022;12(7):668–668; doi: 10.3390/metabo12070668.
27. Pache MM, Pangavhane RR, Dhotre SR, et al. Cognitive Behavioural Therapy: The Treatment of Insomnia and Depression. *Int J Pharm Sci Rev Res* 2024;84(11); doi: 10.47583/ijpsrr.2024.v84i11.005.
28. “Cholinergic Medications.” Sep. 2022. Accessed: Jan.07, 2025. Available: <https://www.ncbi.nlm.nih.gov/books/NBK538163/>
29. Arora S, Santiago JA, Bernstein M, et al. Diet and Lifestyle Impact the Development and Progression of Alzheimer’s Dementia. *Frontiers Media* 2023;10; doi: 10.3389/fnut.2023.1213223.
30. Pan R. Current drug treatments in Alzheimer’s disease. 2023; 36:1492–1498; doi: 10.54097/hset.v36i.6274.
31. Wiesen T, Atlas D. Novel anti-apoptotic L-DOPA precursors SuperDopa and SuperDopamide as potential neuroprotective agents for halting/delaying progression of Parkinson’s disease. *Springer Nature* 2022;13(3); doi: 10.1038/s41419-022-04667-2.
32. Genç ME, Özdamar EN. Dopamine: The Amazing Molecule. *IntechOpen* 2021; doi: 10.5772/intechopen.95444.
33. Luca A, Monastero R, Baschi R, et al. Cognitive impairment and levodopa induced dyskinesia in Parkinson’s disease: a longitudinal study from the PACOS cohort. *Nature Portfolio* 2021;11(1); doi: 10.1038/s41598-020-79110-7.
34. Stocchi F, Bravi D, Emmi A, et al. Parkinson Disease Therapy: Current Strategies and Future Research Priorities. *Nature Portfolio* 2024;20(12):695–707; doi: 10.1038/s41582-024-01034-x.
35. Hörmann P, Delcambre S, Hanke JE, et al. Impairment of neuronal mitochondrial function by l-DOPA in the absence of oxygen-dependent auto-oxidation and oxidative cell damage. *Springer Nature* 2021;7(1); doi: 10.1038/s41420-021-00547-4.
36. Guzman ACV de, Razzak MA, Cho JH, et al. Curcumin-Loaded Human Serum Albumin Nanoparticles Prevent Parkinson’s Disease-like Symptoms in *C. elegans*. *Multidisciplinary Digital Publishing Institute* 2022;12(5):758–758; doi: 10.3390/nano12050758.
37. Fabbrini A, Guerra A. Pathophysiological Mechanisms and Experimental Pharmacotherapy for L-Dopa-Induced Dyskinesia. *Dove Medical Press* 2021; Volume 13:469–485; doi: 10.2147/jep.s265282.
38. Tabrizi SJ, Ghosh R, Leavitt BR. Huntingtin Lowering Strategies for Disease Modification in Huntington’s Disease. *Cell Press* 2019;101(5):801–819; doi: 10.1016/j.neuron.2019.01.039.
39. Khaled HG, Feng H, Hu X, et al. A high-throughput screening to identify small molecules that suppress huntingtin promoter activity or activate huntingtin-antisense promoter activity. *Nature Portfolio* 2021;11(1); doi: 10.1038/s41598-021-85279-2.
40. Badu-Mensah A, Guo X, Hickman JJ. ALS Skeletal Muscle: Victim or Culprit. 2021;2(2); doi: 10.46439/neuroscience.2.012.
41. Brooks BR, Heiman-Patterson T, Wiedau-Pazos M, et al. Edaravone efficacy in amyotrophic lateral sclerosis with reduced forced vital capacity: Post-hoc analysis of Study 19 (MCI186-19) [clinical trial NCT01492686]. *Public Library of Science* 2022;17(6):e0258614–e0258614; doi: 10.1371/journal.pone.0258614.
42. Ouaamari YE, Bos JV den, Willekens B, et al. Neurotrophic Factors as Regenerative Therapy for Neurodegenerative Diseases: Current Status, Challenges and Future Perspectives.

- Multidisciplinary Digital Publishing Institute 2023;24(4):3866–3866; doi: 10.3390/ijms24043866.
43. Omer AB, Dalhat MH, Kaleem M, et al. Butin Mitigates Memory Impairment in Streptozotocin-Induced Diabetic Rats by Inhibiting Oxidative Stress and Inflammatory Responses. Multidisciplinary Digital Publishing Institute 2022;12(11):1050–1050; doi: 10.3390/metabo12111050.
44. Amerika WE, Gaag S van der, Mosch A, et al. Medical and Surgical Treatment for Medication-Induced Tremor: Case Report and Systematic Review. Wiley 2022;9(5):676–687; doi: 10.1002/mdc3.13463.
45. Obadeyi O, Paxton JH, Kouyoumjian S. Benign Presentation Following Massive Deutetrabenazine Overdose. Cureus, Inc 2021; doi: 10.7759/cureus.12886.
46. Hersh AM, Alomari S, Tyler B. Crossing the Blood-Brain Barrier: Advances in Nanoparticle Technology for Drug Delivery in Neuro-Oncology. Multidisciplinary Digital Publishing Institute 2022;23(8):4153–4153; doi: 10.3390/ijms23084153.
47. Mittal K, Pharasi N, Sarna B, et al. Nanotechnology-Based Drug Delivery for the Treatment of CNS Disorders. De Gruyter Open 2022;13(1):527–546; doi: 10.1515/tnsci-2022-0258.
48. Virtanen P, Ortiz K, Patel A, et al. Blood–Brain Barrier Disruption for the Treatment of Primary Brain Tumors: Advances in the Past Half-Decade. Springer Science+Business Media 2024;26(3):236–249; doi: 10.1007/s11912-024-01497-7.
49. “Human Gene Therapy for Neurodegenerative Diseases.” Oct. 2022. Accessed: Jan. 07, 2025. Available: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-neurodegenerative-diseases>
50. Anonymous. Human Gene Therapy for Neurodegenerative Diseases. 2022.
51. Conroy F, Miller R, Alterman JF, et al. Chemical engineering of therapeutic siRNAs for allele-specific gene silencing in Huntington’s disease models. Nature Portfolio 2022;13(1); doi: 10.1038/s41467-022-33061-x.
52. Komatsu H. Innovative Therapeutic Approaches for Huntington’s Disease: From Nucleic Acids to GPCR-Targeting Small Molecules. Frontiers Media 2021;15; doi: 10.3389/fncel.2021.785703.
53. Zamzam AH, Al-Ani A, Wahab AKA, et al. Prioritisation Assessment and Robust Predictive System for Medical Equipment: A Comprehensive Strategic Maintenance Management. Frontiers Media 2021;9(undefined); doi: 10.3389/fpubh.2021.782203.
54. McColgan P, Thobhani A, Boak L, et al. Tominersen in Adults with Manifest Huntington’s Disease. Massachusetts Medical Society 2023;389(23):2203–2205; doi: 10.1056/nejmc2300400.
55. Jagaraj CJ, Parakh S, Atkin JD. Emerging Evidence Highlighting the Importance of Redox Dysregulation in the Pathogenesis of Amyotrophic Lateral Sclerosis (ALS). Frontiers Media 2021;14; doi: 10.3389/fncel.2020.581950.
56. Xu X, Shen D, Gao Y, et al. A Perspective on Therapies for Amyotrophic Lateral Sclerosis: Can Disease Progression Be Curbed? BioMed Central 2021;10(1); doi: 10.1186/s40035-021-00250-5.
57. Ranieri F, Mariotto S, Dubbioso R, et al. Brain Stimulation as a Therapeutic Tool in Amyotrophic Lateral Sclerosis: Current Status and Interaction With Mechanisms of Altered Cortical Excitability. Frontiers Media 2021;11; doi: 10.3389/fneur.2020.605335.
58. Parmar V, Patel G, Abu-Thabit NY. Responsive Cyclodextrins as Polymeric Carriers for Drug Delivery Applications. In: Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications, Volume 1 Elsevier; 2018; pp. 555–580; doi: 10.1016/B978-0-08-101997-9.00024-2.
59. Barbuti PA, Barker RA, Brundin P, et al. Recent Advances in the Development of Stem-Cell-Derived Dopaminergic Neuronal Transplant Therapies for Parkinson’s Disease. Wiley 2021;36(8):1772–1780; doi: 10.1002/mds.28628.
60. Anonymous. Experimental and Clinical Transplantation. Başkent University 2024; doi: 10.6002/ect.
61. Yue C, Feng S, Chen Y, et al. The Therapeutic Prospects and Challenges of Human Neural Stem Cells for the Treatment of Alzheimer’s Disease.

- Springer Nature 2022;11(1); doi: 10.1186/s13619-022-00128-5.
62. Balusu S, Horré K, Thrupp N, et al. MEG3 activates necroptosis in human neuron xenografts modeling Alzheimer's disease. *American Association for the Advancement of Science* 2023;381(6663):1176–1182; doi: 10.1126/science.abp9556.
63. Cha Y, Park TY, Leblanc P, et al. Current Status and Future Perspectives on Stem Cell-Based Therapies for Parkinson's Disease. *Korean Movement Disorders Society* 2023;16(1):22–41; doi: 10.14802/jmd.22141.
64. Deguchi K, Zambaiti E, Coppi PD. Regenerative Medicine: Current Research and Perspective in Pediatric Surgery. Springer Science+Business Media 2023;39(1); doi: 10.1007/s00383-023-05438-6.
65. Scannevin RH. Therapeutic Strategies for Targeting Neurodegenerative Protein Misfolding Disorders. Elsevier BV 2018; 44:66–74; doi: 10.1016/j.cbpa.2018.05.018.
66. Ilyasu MO, Musa SA, Oladele SB, et al. Amyloid-Beta Aggregation Implicates Multiple Pathways in Alzheimer's Disease: Understanding the Mechanisms. *Frontiers Media* 2023;17; doi: 10.3389/fnins.2023.1081938.
67. Gonzales MM, Garbarino VR, Kautz TF, et al. Senolytic therapy in mild Alzheimer's disease: a phase 1 feasibility trial. *Nature Portfolio* 2023;29(10):2481–2488; doi: 10.1038/s41591-023-02543-w.
68. Siwecka N, Saramowicz K, Galita G, et al. Inhibition of Protein Aggregation and Endoplasmic Reticulum Stress as a Targeted Therapy for α -Synucleinopathy. *Multidisciplinary Digital Publishing Institute* 2023;15(8):2051–2051; doi: 10.3390/pharmaceutics15082051.
69. Chakrabarti S, Bisaglia M. Oxidative Stress and Neuroinflammation in Parkinson's Disease: The Role of Dopamine Oxidation Products. *Multidisciplinary Digital Publishing Institute* 2023;12(4):955–955; doi: 10.3390/antiox12040955.
70. Herrmann F, Heßmann M, Schaertl S, et al. Pharmacological characterization of mutant huntingtin aggregate-directed PET imaging tracer candidates. *Nature Portfolio* 2021;11(1); doi: 10.1038/s41598-021-97334-z.
71. Saravanan J, Krishnamurthy PT. Role of Microgliosis, Oxidative Stress and Associated Neuroinflammation in the Pathogenesis of Parkinson's Disease: The Therapeutic Role of Nrf2 Activators. Elsevier BV 2021; 145:105014–105014; doi: 10.1016/j.neuint.2021.105014.
72. Territo PR, Zarrinmayeh H. P2X7 Receptors in Neurodegeneration: Potential Therapeutic Applications from Basic to Clinical Approaches. *Frontiers Media* 2021;15; doi: 10.3389/fncel.2021.617036.
73. Iarlori C. Anti-Inflammatory Agents in Parkinson's Disease. Bentham Science Publishers 2009;8(1):72–84; doi: 10.2174/187152309787580757.
74. Ellis-Behnke R, Teather LA, Schneider GE, et al. Using Nanotechnology to Design Potential Therapies for CNS Regeneration. Bentham Science Publishers 2007;13(24):2519–2528; doi: 10.2174/138161207781368648.
75. Lee K-W, Yam JWP, Mao X. Dendritic Cell Vaccines: A Shift from Conventional Approach to New Generations. *Multidisciplinary Digital Publishing Institute* 2023;12(17):2147–2147; doi: 10.3390/cells12172147.
76. Mancinelli C, Rossi ND, Capra R. Ocrelizumab for the Treatment of Multiple Sclerosis: Safety, Efficacy, and Pharmacology. Dove Medical Press 2021; Volume 17:765–776; doi: 10.2147/term.s282390.
77. Libon DJ, Baliga G, Swenson R, et al. Digital Neuropsychological Assessment: New Technology for Measuring Subtle Neuropsychological Behavior. IOS Press 2021;82(1):1–4; doi: 10.3233/jad-210513.
78. Rahman MM, Islam MR, Islam MT, et al. Stem Cell Transplantation Therapy and Neurological Disorders: Current Status and Future Perspectives. *Multidisciplinary Digital Publishing Institute* 2022;11(1):147–147; doi: 10.3390/biology11010147.
79. Nand S, Singh P, Varshney R, et al. Promising Drug Targets and Associated Therapeutic Interventions in Parkinson's Disease. *Medknow* 2021;16(9):1730–1730; doi: 10.4103/1673-5374.306066.

80. Baweja GS, Gupta S, Kumar B, et al. Recent Updates on Structural Insights of MAO-B Inhibitors: A Review on Target-Based Approach. Springer Science+Business Media 2023;28(3):1823–1845; doi: 10.1007/s11030-023-10634-6.
81. Jiang X, Li S, Feng X, et al. Mushroom Polysaccharides as Potential Candidates for Alleviating Neurodegenerative Diseases. Multidisciplinary Digital Publishing Institute 2022;14(22):4833–4833; doi: 10.3390/nu14224833.
82. Jarosińska OD, Rüdiger S. Molecular Strategies to Target Protein Aggregation in Huntington's Disease. Frontiers Media 2021;8; doi: 10.3389/fmolb.2021.769184.
83. Youdim MBH. Why Do We Need Multifunctional Neuroprotective and Neurorestorative Drugs for Parkinson's and Alzheimer's Diseases as Disease Modifying Agents? 2010;19(1):1–14; doi: 10.5607/en.2010.19.1.1.
84. Sadique M, Mohit M, Kaur G, et al. Mini-review on personalized medicine: a revolution in health care. 2021;3(4):16–16; doi: 10.53388/pmr2021080601.
85. Wiedermann CJ. Advancing Precision Medicine in South Tyrol, Italy: A Public Health Development Proposal for a Bilingual, Autonomous Province. Multidisciplinary Digital Publishing Institute 2023;13(6):972–972; doi: 10.3390/jpm13060972.
86. Qureshi R, Irfan M, Gondal TM, et al. AI in Drug Discovery and Its Clinical Relevance. Elsevier BV 2023;9(7):e17575–e17575; doi: 10.1016/j.heliyon.2023.e17575.
87. Catacutan DB, Alexander J, Arnold A, et al. Machine Learning in Preclinical Drug Discovery. Nature Portfolio 2024;20(8):960–973; doi: 10.1038/s41589-024-01679-1.
88. Pache MM, Pangavhane RR, Jagtap MN, et al. The AI-Driven Future of Drug Discovery: Innovations, Applications, and Challenges. 2025; doi: 10.52711/2231-5659.2025.00009.
89. Duan L, Li X, Ji R, et al. Nanoparticle-Based Drug Delivery Systems: An Inspiring Therapeutic Strategy for Neurodegenerative Diseases. Multidisciplinary Digital Publishing Institute 2023;15(9):2196–2196; doi: 10.3390/polym15092196.
90. Meyer AH, Feldsien TM, Mezler M, et al. Novel Developments to Enable Treatment of CNS Diseases with Targeted Drug Delivery. Multidisciplinary Digital Publishing Institute 2023;15(4):1100–1100; doi: 10.3390/pharmaceutics15041100.
91. Nie L, Yao D, Chen S, et al. Directional Induction of Neural Stem Cells, a New Therapy for Neurodegenerative Diseases and Ischemic Stroke. Springer Nature 2023;9(1); doi: 10.1038/s41420-023-01532-9.
92. Li J, Luo W, Xiao C, et al. Recent Advances in Endogenous Neural Stem/Progenitor Cell Manipulation for Spinal Cord Injury Repair. Ivyspring International Publisher 2023;13(12):3966–3987; doi: 10.7150/thno.84133

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