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Comprehensive Review of Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis, represent a significant and growing global health challenge, particularly with aging populations. This review synthesizes current understanding, tracing the historical recognition of these conditions to the complex molecular mechanisms now known to drive neuronal loss. Key pathogenic processes discussed include protein misfolding and aggregation (e.g., amyloid-beta, tau, alpha-synuclein, mutant huntingtin), oxidative stress linked to mitochondrial dysfunction (often exacerbated by genetic factors like SOD1 mutations), chronic neuroinflammation involving glial activation (microglia and astrocytes), and disruptions in proteostasis, particularly impaired autophagy. While current treatments remain largely symptomatic, offering temporary relief (e.g., cholinesterase inhibitors/memantine for Alzheimer's disease, levodopa for Parkinson's disease), the focus is shifting towards disease-modifying strategies. This review highlights progress in immunotherapies targeting protein aggregates (like Lecanemab /Donanemab for amyloid-beta, Prasinezumab for alpha-synuclein), gene-targeted therapies using antisense oligonucleotides (Tofersen for SOD1) and CRISPR/Cas9 systems (preclinical work on HTT and C9orf72) and stem cell approaches using induced pluripotent stem cells. Diagnostic innovations, including advanced PET imaging, fluid biomarkers (CSF Aβ/tau, blood NfL), and digital biomarkers, are improving early detection and monitoring. Despite these advances, significant challenges such as disease heterogeneity, blood-brain barrier penetration, biomarker limitations, and socioeconomic/ethical hurdles impede clinical translation. Future directions emphasize personalized medicine, multi-target therapies (multi-target direct ligands, combinations), repurposed drugs (Exenatide, Pridopidine), natural compounds (Curcumin, Pingchan granule), pathway modulation (mTOR inhibitors), and preventive strategies.

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INTRODUCTION

The history of neurodegenerative disorders dates back to ancient times, where they have been a challenge to human health throughout the ages [1]. Neurodegenerative disorders affected approximately 15% of worldwide population, furthermore, it is anticipated that throughout the next 20 years, the burden of chronic neurodegenerative

diseases would at least double. Maintaining universal access to neurological care will be extremely difficult as a result of this development, which is mostly attributable to the growing aging population [2]. While high income countries report higher prevalence, low resource regions face rising cases with limited treatment access exacerbating global disparities [3]. Neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson disease (PD), Amyotrophic lateral sclerosis and Huntington disease (HD) pose a profound to global public health system. This condition shares a common hallmark: the gradual deterioration of nerve cells over time which manifests in devasting physical, cognitive and psychological impairments [4]. As global demographics shift toward older population the trend projected to intensify over the coming decades, the prevalence of these disorders is expected to rise sharply [5]. Despite decades of research existing treatment remain largely palliative offering limited relief for symptoms without addressing the root causes of neuronal loss [6]. This gap underscores the urgent need to unravel the biological mechanisms driving neurodegeneration and translate this insight into therapies capable of altering disease trajectories [7]. Recent advances in molecular biology and neuroimaging have begun to illuminate the complex interplay of genetic, environmental and cellular factors contributing to these diseases. For instance, studies highlight the role of protein misfolding [8], mitochondrial dysfunction [9], and neuroinflammation [10] in disrupting neural networks. Meanwhile innovative diagnostic tools such as biomarkers identification [11], and advanced imaging technique e.g. tau-PET scan [12], are enabling earlier and more accurate detection opening windows for timely intervention. On therapeutic front emerging strategies including gene editing [13], stem cell therapy [14] and targeted immunomodulation [15] show promise in preclinical models though clinical translation remains fraught with challenges such as blood brain barrier penetration [16]. This review synthesizes current knowledge on history of neurodegenerative disorders, molecular pathways, therapeutic innovations, diagnostic advancements, and persistent challenges.

HISTORY OF NEURODEGENERATIVE DISORDERS

Early Observations common signs and symptoms of neurodegenerative diseases were described in ancient medical writings from Greece and China and other ancient civilizations but there was no clear understanding or description of these conditions [1]. In 19th century Dr. James Parkinson originally referred to Parkinson's disease (PD) as "shaking palsy" in 1817. This was based on his observations of a group of clinical manifestations in six individuals, which he compiled in his publication "An Essay on the Shaking Palsy" [17]. The scientific community did not take Dr. Parkinson's findings seriously until over a century later, when French neurologist Jean-Martin Charcot, who was greatly interested in Dr. Parkinson's work, brought up the topic of shaking palsy in a lecture on June 12, 1988 [18]. North American general practitioner George Huntington published in The Medical and Surgical Reporter in 1872. His article was simply titled "On Chorea" and it quickly gained widespread acceptance that this particular kind of chorea constituted a special hereditary illness, leading to the development of Huntington's disease (HD) [19]. In 20th century Alois Alzheimer made the ground-breaking discovery of the pathological characteristics of Alzheimer's disease at the beginning of the 20th century [20]. Throughout the nineteenth and the first part of the twentieth centuries, there was a pervasive and unreasonable fear of degeneration. This fear serves as a reminder that words can have a powerful effect and should be chosen

carefully. It also contributed to the introduction of eugenic measures in several Western societies [21]. the first writer of a medical article whose title contains the adjective neurodegenerative. A British journal published it in 1965 [22]. Between 1960 and 1990, research focused on the role of neurotransmitters in neurodegenerative diseases, such as the role of Dopamine in Parkinson's disease, GABA in Huntington's disease, and Acetylcholine in Alzheimer's disease. During the same time period, research was being conducted to study protein aggregates in neurodegenerative diseases. In the last few years, significant study has focused on how and why aggregation happens and what may be done to avoid illnesses [23].

MECHANISMS UNDERLYING NEURODEGENERATION

Protein Aggregation and Misfolding

A hallmark of neurodegenerative diseases is the accumulation of misfolded proteins, which form toxic aggregates that disrupt cellular function. In AD, amyloid-beta (Aβ) plaques and hyperph osphorylated tau neurofibrillary tangles impair synaptic communication and induce neuronal death [24]. Senile plaques are extracellular deposits of beta-amyloid protein (Aβ), with different morphological forms such as neuritic, diffuse, dense-cored, and compact type plaques. These plaques are formed through proteolytic cleavage by enzymes like β-secretase and γ-secretase, leading to Aβ40 and Aβ42 fragments. Additionally, Aβ monomers can form large insoluble amyloid fibrils or soluble oligomers, which spread throughout the brain and contribute to neurotoxicity. This accumulation leads to activation of astrocytes and microglia, damaging axons, dendrites, and causing synapse loss, resulting in cognitive impairments [24]. Similarly, accumulation of α-synuclein aggregates in the substantia nigra pars compacta is central in Parkinson's disease pathophysiology, disrupting dopamine production, causing dopaminergic neuron degeneration, and leading to motor dysfunction [25]. In Huntington's disease (HD) mutant huntingtin (mHTT) leads to the loss of striatal neurons, contributing to neuronal dysfunction and motor symptoms [26]. These aggregates propagate through prion-like mechanisms, seeding pathology in neighbouring cells [27].

Oxidative Stress and Mitochondrial Dysfunction

Excessive production of reactive oxygen species (ROS) outpaces the body antioxidant defences, causing widespread damage to lipids, proteins, and DNA. In ALS, mitochondrial dysfunction amplifies this oxidative stress, particularly due to mutations in the SOD1 gene. These mutations not only cripple ROS detoxification but also trigger toxic interactions within mitochondria, worsening cellular harm [28]. Furthermore, RNA-binding proteins like TDP-43 and FUS disrupt mitochondrial stability—either by altering their structural dynamics or binding directly to mitochondrial components—creating a self-sustaining cycle of oxidative injury [28]. In Parkinson's disease (PD), mitochondrial complex I deficiency disrupts ATP synthesis and elevates reactive oxygen species (ROS), overwhelming antioxidant defences. This oxidative stress—driven by DJ1 mutations, calcium-dependent pacemaking, and dopamine metabolism—triggers lysosomal dysfunction and dopaminergic neuron degeneration via lipid peroxidation and protein misfolding [29].

Neuroinflammation and Glial Activation

In neurodegeneration, microglia and astrocytes transition from protective roles to chronic activation (M1/A1 states), releasing TNF-α and IL-1β. This sustains

neuroinflammation by impairing clearance of protein aggregates and activating the complement system, driving synaptic loss and neuronal damage [30]. For example, in AD, TREM2 mutations impair microglial phagocytic activity by reducing TREM2–Aβ binding, leading to defective amyloid clearance. This accelerates Aβ accumulation and tau seeding. Concurrently, TREM2 drives the differentiation of disease-associated microglia (DAM), a neuroprotective state that mitigates Aβ toxi city through enhanced phagocytic and anti-inflammatory functions [31]. In Parkinson's disease, mitochondrial complex I deficiency reduces ATP and elevates mitochondrial ROS, priming NLRP3 inflammasome activation. This is exacerbated by α-synuclein aggregates binding TLRs, triggering microglial NLRP3 assembly. Resultant IL-1β release and caspase-1 activation accelerate dopaminergic neuron loss via oxidative stress and lysosomal dysfunction [23].

Genetic and Epigenetic Contributions

Genetic mutations play a central role in inherited neurodegenerative diseases. For instance, mutations in APP and PSEN1/2 disrupt amyloid-β clearance in Alzheimer's, while LRRK2 and PINK1 defects in Parkinson's hinder mitochondrial repair and lysosomal function. In ALS and FTD, C9orf72 expansions create toxic RNA clusters, whereas Huntington's is driven by CAG repeats in huntingtin, which form damaging protein aggregates. These mutations converge on shared pathways—like oxidative stress and faulty autophagy—worsening neuronal loss. Familial cases reveal how protein misfolding and inflammation underpin neurodegeneration [7]. In neurodegenerative diseases like Huntington's, disrupted DNA methylation and histone acetylation synergistically drive gene dysregulation. HDAC inhibitors counter hypoacetylation, restoring transcriptional balance and neuroprotection by enhancing neurite growth and reducing toxic aggregates, offering therapeutic potential across Alzheimer's, Parkinson's, and depression [33,34].

Disrupted Proteostasis and Autophagy

Chaperone -mediated autophagy (CMA) play a vital role in preserving cellular balance by breaking down damaged and misfolded proteins, in neurodegeneration condition, particularly in their later stages, CMA activity decrease so occur buildup of harmful proteins aggregates and cellular dysfunction. This impairment is linked to progression of neurodegenerative diseases. Researches indicate that enhancing CMA function could offer promising therapeutic approach to help manage and slow progression of these disorders [35].

CURRENT THERAPEUTIC STRATEGIES

Symptomatic Treatments

Existing therapies focus on symptom management:

- **AD**: Acetylcholinesterase inhibitors (donepezil, IVL3003 and GB-5001) and NMDA antagonists (memantine, AVP-786, AXS-05) temporarily improve cognition [36].
- **PD**: Levodopa replenishes dopamine but loses efficacy with disease progression [29].
- **HD**: Tetrabenazine, a dopamine-depleting agent, significantly reduces Huntington's chorea but worsens functional outcomes and fails to halt neurodegeneration. While neuroleptics and anti-glutaminergic therapies show inconsistent efficacy, high-quality RCTs remain scarce, underscoring the urgent need for trials targeting non-

motor symptoms like neuropsychiatric decline [37].

DISEASE-MODIFYING APPROACHES

Immunotherapies

The recent approval of Lecanemab and Donanemab marks a pivotal shift in Alzheimer's treatment. These monoclonal antibodies target amyloid-β (Aβ), with Lecanemab gaining FDA approval in early 2023 after demonstrating reduced amyloid plaques and delayed cognitive decline. By activating microglia to clear Aβ and promoting its removal from the brain, they also curb tau pathology—a key downstream effect. While earlier approaches like Aβ vaccines faltered, these therapies validate the amyloid hypothesis, offering tangible hope. However, challenges like accessibility and long-term safety risks, including brain swelling, underscore the need for continued research to optimize their impact [38]. Another antibody is semorinemab which is targeting tau aggregation, aiming to slow cognitive decline by inhibiting the formation of toxic aggregates, with varying results depending on the stage of the disease [39]. Similarly, PD trials are testing antibodies against α-synuclein (Prasinezumab) which is a monoclonal antibody that binds aggregated α-synuclein at the C-terminal of the protein, being investigated in early-stage Parkinson's disease [40].

Gene-Targeted Therapies

ASOs and RNAi: Tofersen, an antisense oligonucleotide (ASO) targeting SOD1, reduces CSF biomarkers in ALS. Under investigation for ALS caused by SOD1 mutations, Tofersen works by promoting RNase H–dependent degradation of SOD1 mRNA, thereby decreasing SOD1 protein production [41]. Huntingtin-lowering ASOs (e.g., RG6042) are in phase I/IIa trials for HD (26). CRISPR/Cas9 has demonstrated significant potential in preclinical studies for editing the mutant HTT gene in Huntington's disease (HD) and the C9orf72 gene in amyotrophic lateral sclerosis (ALS). The GGGGCC24+ hexanucleotide repeat expansion in the C9ORF72 gene is recognized as a major genetic contributor to ALS and frontotemporal dementia (FTD), while CAG repeat expansions in the HTT gene lead to the development of Huntington's disease. Notably, CRISPR/Cas9 technology has proven effective in excising the C9ORF72 repeat expansion from primary cortical neurons, mouse brains, and patient-derived iPSC motor neurons. In HD models, CRISPR-Cas9 intervention resulted in the disruption of the mutant HTT gene, leading to a significant reduction in neuronal inclusions, as well as notable improvements in motor functions and lifespan, highlighting its therapeutic promise for these debilitating neurodegenerative disorders [42,43].

Stem Cell Therapies

Induced pluripotent stem cells (iPSCs) differentiate into dopaminergic neurons for PD and motor neurons for ALS. Despite their promise, challenges remain in ensuring the survival and integration of these cells and avoiding tumour formation. Using iPSCs derived from a patient's own cells eliminates the risk of immune rejection. Ongoing trials, such as those by GForce-PD, are crucial to demonstrating the safety and effectiveness of iPSC-based therapies for neurodegenerative diseases [44].

REPURPOSED DRUGS AND SMALL MOLECULES

- **NLRP3 Inhibitors**: MCC950 reduces neuroinflammation in AD models. It works by inhibiting the activation of the NLRP3 inflammasome, a key player in AD pathology. This inhibition helps to mitigate the chronic neuroinflammatory responses

that contribute to cognitive impairment in AD. The effects of MCC950 have been observed both in vivo in animal models and in vitro, where it reduces autophagy and the activation of pro-inflammatory cytokines, providing a neuroprotective effect [45].

- **PPAR-γ Agonists**: Pioglitazone enhances mitochondrial function in PD trials by ramping up Paraoxonase-2 (PON2), a key enzyme that combats oxidative damage. While PON2 strengthens mitochondria by neutralizing harmful free radicals and stabilizing energy production, its effects fade within weeks, underscoring the challenge of sustaining antioxidant defences in neurodegenerative therapies [46].

Non-Pharmacological Interventions

- **Exercise**: Aerobic activity boosts brain-derived neurotrophic factor (BDNF), improving cognition in AD by enhancing synaptic plasticity and neuroprotection [47].
- **Diet**: Ketogenic diets reduce oxidative stress in HD models by enhancing mitochondrial function and improving neuronal survival [48].

DIAGNOSTIC AND BIOMARKER INNOVATIONS

Imaging Biomarkers

- **Amyloid- and Tau-PET**: Detect AD pathology years before symptoms enabling early intervention strategies and improving outcomes in clinical trials [49].
- **DaTSCAN**: Visualizes dopaminergic loss in PD aiding diagnosis and differentiating from other movement disorders effectively [29].

Fluid Biomarkers

- **CSF Aβ42/tau Ratio**: Predicts AD progression, guiding early interventions [49].
- **Blood Neurofilament Light (NfL)**: Serves as a sensitive biomarker for axonal damage in ALS and Huntington's disease (HD). Advanced assays (e.g., electrochemiluminescence, single-molecule arrays) now enable precise blood NfL measurement, reflecting neurodegeneration severity. Elevated NfL correlates with disease progression and treatment response, extending its utility to MS, dementia, and Parkinson's [50].

DIGITAL BIOMARKERS

The accelerometer derived vertical movement index (VMI) reliably distinguished different rates of ALS progression and showed a strong link with overall survival. These results suggest that incorporating addclerometry into clinical trials may be offer more object, sensitive way to monitor disease progression and treatment effects [51]. In PD digital biomarkers are rapidly advancing in both motor and non-motor domains, motor biomarkers show significant effectiveness in assessing progression of disease, while non motor biomarkers such ad measuring autonomic function are still require validation for effectiveness in early stages of disease [52]. The digital cognitive biomarkers (DCBs), derived from hierarchical Bayesian cognitive process (HBCP) models, have shown effectiveness in distinguishing individuals at risk of imminent cognitive decline from those without such risk even when both groups are classified as cognitively normal. This highlights their potential for early detection of Alzheimer's related changes [53].

CHALLENGES IN TRANSLATION AND CLINICAL PRACTICE

Heterogeneity of Disease

Neurodegenerative disorders like frontotemporal dementia (FTD) and Alzheimer's disease (AD) are biologically heterogeneous, resulting in high variability in in vivo disease biomarkers like volumetric measurements from imaging, protein measurements from lumbar puncture, and behavioral measurements from psychometrics. This limits their utility in disease studies and management. Individuals with diverse disease subtypes and stages of the illness process contribute to phenotypic and temporal variability, respectively [54].

Blood-Brain Barrier (BBB) Penetrance

In contrast to other human organs, the brain is a sensitive portion of the body. Despite numerous improvements in this field, brain-specific medication delivery remains a difficult issue in the pharmaceutical industry. This is mostly owing to the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB). Various formulations serving as brain-drug delivery systems are available, which are effective but have lower efficiency in treating CNS illnesses [55].

Biomarker Limitations

Lack of validated biomarkers for early diagnosis and trial endpoints delays drug approval. Initiatives like the Alzheimer's Disease Neuroimaging Initiative (ADNI) address this gap [56].

Ethical and Socioeconomic Barriers

Neurodegenerative diseases like Alzheimer's impose a massive financial burden on European countries. In France annual dementia care costs average €8,892 per patient, while Germany and the UK report monthly costs of €2,349 and €2,016, respectively, with informal family care covering 50–61% of total expenses. Europe's total dementia costs hit €238.6 billion in 2010, projected to rise to €343 billion by 2050. However, inconsistent cost-calculation methods, scarce epidemiological data, and reliance on UN demographic projections (with error margins up to 100%) undermine accuracy. Despite national strategies to combat dementia, the lack of standardized cost monitoring and data collection complicates policy efforts to address this escalating crisis [57]. Ethical challenges in neurological therapies centre on informed consent, equity, and oversight. Vulnerable populations, such as dementia patients, face difficulties in providing autonomous consent for gene-editing trials. Cognitive enhancements risk widening social disparities if access is limited to privileged groups. Current regulatory frameworks lag behind innovations like immunotherapies and gene therapies, creating gaps in monitoring dual-use risks (e.g., non-medical genetic modifications). Ethical frameworks emphasize patient-centered care, data transparency, and global collaboration to harmonize standards. Balancing rapid scientific progress with equitable access and patient safety remains critical, necessitating inclusive policies and adaptive governance [58].

FUTURE DIRECTIONS

Personalized Medicine

Integration of genomics, proteomics, and AI-driven models will enable subtype-specific therapies. For example, bapineuzumab which is an antibody target amyloid-beta show increase in their activity with patients with APOE ε4 carriers in AD [59].

Multitarget therapies

Traditional single target therapies often failed due to the complex interplay of neurodegeneration mechanisms so combining anti-aggregation, anti-inflammatory, and pro-autophagy agents may address multifactorial pathology. For examples

Multi-Target Direct Ligands (MTDLs)

AD: Ladostigil a multimodal drug designed to treat (AD) and dementia combines the MAO-B inhibitory propargyl moiety of rasagiline with the cholinesterase inhibiting carbamate group of rivastigmine. This dual mechanism simultaneously targets oxidative stress (via MAO-B inhibition) and enhances cholinergic function (via AChE/BuChE inhibition). Preclinical studies demonstrate its neuroprotective effects, including reduced amyloid-beta accumulation and improved cognitive function. Currently in Phase IIb trials, ladostigil aims to address multiple neurodegenerative pathways while minimizing side effects, offering a promising therapeutic strategy for complex neurological disorders [60]. Methylthioninium chloride (MB) targets tau aggregation and oxidative stress by inhibiting tau polymer growth and inducing autophagy, evidenced by reduced p62 and elevated LC3-II/BECN1 in preclinical models. In transgenic mice, MB decreased hyperphosphorylated tau but showed inconsistent effects on insoluble aggregates, possibly due to dosing limitations. Mechanistically, MB modulates mTOR/Akt/GSK-3β signaling—similar to rapamycin—reducing mTOR activity while paradoxically increasing Akt phosphorylation, ultimately suppressing tau phosphorylation and enhancing autophagic clearance. These dual pathways highlight MB potential to disrupt tau pathology, though clinical translation requires optimizing brain bioavailability and addressing variability in preclinical outcomes [61].

PD: Rasagiline MAO-B inhibition and anti-apoptotic properties. Rasagiline's dual mechanisms in Parkinson's disease involve MAO-B inhibition and anti-apoptotic activity. By blocking MAO-B, it preserves dopamine levels, alleviating motor symptoms. Independently, its propargyl group activates cellular pathways (e.g., Bcl-2, PKC) that inhibit neuronal apoptosis, even without MAO-B inhibition. Preclinical models show this propargyl-driven neuroprotection reduces oxidative stress and toxin-induced cell death [62].

Combination Therapies

AD: Donepezil (acetylcholinesterase inhibitor) combined with memantine (NMDA antagonist). Donepezil enhances cognition by inhibiting acetylcholinesterase and elevating synaptic acetylcholine to improve memory and learning. Memantine counters glutamate toxicity via NMDA receptor blockade, reducing calcium overload and neuronal apoptosis. Together, they synergistically stabilize synaptic function: Donepezil boosts cholinergic signalling while Memantine prevents excitotoxic damage. This dual action mitigates amyloid- and tau-driven neurodegeneration and dampens neuroinflammation. Clinically, their combination delays cognitive decline more effectively than either drug alone, though dose-dependent side effects (e.g., nausea, dizziness) may arise from prolonged cholinergic-glutamatergic modulation. Balancing efficacy and safety remain critical [63].

ALS: Edaravone combined with riluzole. Edaravone a free-radical scavenger,

combats oxidative stress by neutralizing lipid peroxides in ALS while riluzole modulates glutamate excitotoxicity via sodium channel blockade and mitochondrial stabilization. Combined they synergistically slow motor decline. Edaravone preserves neuronal integrity and riluzole reduces hyperexcitability [64].

Repurposed drugs

PD: Exenatide (GLP-1 agonist) appears to help people with PD move better. A study observed that individuals with moderate Parkinson's who took exenatide for nearly a year showed a noticeable improvement in their motor skills when they were assessed without their usual PD medication. This improvement was still apparent even after they had stopped taking exenatide for three months. The potential reason behind this positive effect could be linked to how exenatide works within the body. Research suggests it might improve the health of mitochondria which are like the powerhouses of cells, and also reduce inflammation. These effects are thought to be important in Parkinson's disease and could explain why exenatide seems to lead to better motor function [65].

HD: Pridopidine primary mechanism in HD appears to be modulating sigma-1 receptors (S1R) rather than its initially proposed dopamine receptor interaction. S1R is a vital protein involved in maintaining cellular health, including protein folding, calcium balance, and neuronal survival. Research confirms pridopidine binds much more strongly to S1R. This engagement activates neuroprotective pathways disrupted in HD. Laboratory studies demonstrate pridopidine protects nerve cells against mutant huntingtin toxicity, improves neuronal connections, regulates calcium signalling reduces harmful protein aggregates and boosts brain-derived neurotrophic factor (BDNF). These beneficial effects are consistently shown to depend on S1R activity [66].

NATURAL COMPOUNDS

There are many studies that have proven the effectiveness of natural substances or their extracts in protecting or treating neurodegenerative disorders, for example: Curcumin, a compound found in turmeric shows promise in tackling key aspects of Alzheimer's Disease. One major way it works is by targeting amyloid-beta, the protein that forms plaques in the brains of AD patients. Studies suggest curcumin can help break down existing amyloid plaques and prevent new ones from forming. It seems to destabilize the amyloid protein itself and also block its ability to clump together. Beyond this, curcumin acts as a protector against inflammation and oxidative stress, both of which are damaging in Alzheimer's. It has anti-inflammatory properties, reducing levels of harmful inflammatory molecules in the brain. Furthermore, curcumin exhibits antioxidant activity, helping to counteract oxidative stress by boosting antioxidant enzymes and stabilizing damaging free radicals. These combined actions against amyloid-beta, inflammation, and oxidative stress – are why curcumin is being actively researched for its potential benefits in AD [67]. Pingchan granule (PCG) is a traditional Chinese medicine formulation used for decades to treat Parkinson's Disease (PD) in China. Based on clinical practice PCG is reported to alleviate both motor symptoms (like slowed movement and tremor) and non-motor issues (such as depression and cognitive decline) associated with PD, complementing standard therapies with low toxicity. Despite these reported benefits, previous evidence lacked rigor due to small study sizes. Recognizing that PD progression can be rapid in earlier stages, the research described aims to provide stronger evidence by conducting a larger, well-controlled clinical trial to formally evaluate

PCG's efficacy and safety specifically in patients with non-advanced PD [68].

GENE AND PATHWAY MODULATION

In ALS mouse models, using adeno-associated virus to deliver CRISPR/Cas9, researchers successfully disrupted the faulty SOD1 gene. This genome editing lowered levels of the harmful protein, resulting in the mice having better movement, later disease onset, and longer survival, highlighting CRISPR potential as a direct gene therapy [69]. Inhibiting mTOR early in Huntington's models enhances autophagy. This treatment restored normal lysosome levels and reduced clumps of disease-related proteins like mutant huntingtin protein (mHTT), p62 and ubiquitin, suggesting benefits from stimulating cellular cleanup early in the disease [70].

PREVENTIVE STRATEGIES

Early interventions targeting modifiable risk factors (hypertension, obesity) could delay disease onset [47].

CONCLUSION

This review highlights the substantial progress made in understanding the multifaceted nature of neurodegenerative disorders, moving from historical observations to detailed molecular insights. Key mechanisms, including protein aggregation, oxidative stress, neuroinflammation, and genetic contributions, are now better understood, paving the way for more targeted therapeutic strategies. While symptomatic treatments offer limited relief, the development of disease-modifying approaches like immunotherapies targeting specific proteins (Aβ, tau, α-synuclein) and gene-based therapies (ASOs, CRISPR) marks a significant advancement. Diagnostic tools, particularly biomarkers from imaging and fluids, are enhancing early detection. However, significant challenges remain, including overcoming the blood-brain barrier, addressing disease heterogeneity, validating biomarkers, and navigating ethical and economic barriers. Future efforts focusing on personalized medicine, multi-target agents, combination therapies, repurposed drugs, and modulating specific pathways like autophagy hold considerable promise for developing treatments that can truly alter the course of these devastating diseases, emphasizing the continued need for rigorous research and clinical translation.

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CONFLICT OF INTEREST

The researchers not have conflict of interest

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