Integrative Insights into Neuropharmacology, Experimental Screening, and Emerging Therapeutic Innovations in Neurodegenerative Disorders: A Comprehensive Review

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Abstract

Background:
Neurodegenerative diseases (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) impose immense social and clinical burdens. Their progressive neuronal loss results from diverse mechanisms including protein aggregation, mitochondrial dysfunction, neuroinflammation, and genetic mutations. Neuropharmacology seeks to elucidate how drugs influence neuronal function and behavior to discover novel therapeutic agents. **Aim:** This review consolidates current knowledge on neuropharmacological mechanisms, preclinical screening and animal modeling approaches, and recent advances in molecular and cellular therapeutics for NDs. **Methods:** Peer-reviewed literature from 2000–2025 was surveyed via PubMed, Scopus, and Web of Science databases using keywords: *neuropharmacology*, *neurodegenerative disease*, *animal models*, *antisense oligonucleotides*, *gene therapy*, and *neuromodulation*. Articles on molecular mechanisms, preclinical assays, clinical translation, and regulatory approvals were critically analyzed. **Results:** Neuropharmacological studies have revealed multiple therapeutic targets, including neurotransmitter systems, oxidative stress, neuroinflammatory signaling, and protein aggregation pathways. A wide spectrum of animal screening methods behavioral, biochemical, histological, and imaging-based continues to guide preclinical evaluation. Rapid progress in antisense oligonucleotides (ASOs), adeno-associated viral (AAV) gene therapy, CRISPR-based genome editing, stem cell therapy, and monoclonal antibodies marks a paradigm shift in ND management. **Conclusions:** Modern neuropharmacology integrates mechanistic insight, preclinical modeling, and cutting-edge biotechnologies to achieve disease modification in previously intractable conditions. Translational fidelity, precision biomarkers, and ethical frameworks will determine the future success of these strategies.

Keywords: Neuropharmacology; Animal models; Behavioral screening; Gene therapy; Antisense oligonucleotides;

1. Introduction

Neurodegenerative diseases (NDs) represent a heterogeneous group of chronic, progressive disorders characterized by selective neuronal loss within defined regions of the central nervous system (CNS) [1]. Major examples include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and spinal muscular atrophy (SMA). Collectively, they affect more than 50 million individuals worldwide, with global incidence projected to double by 2050 [2].

Pathogenetic mechanisms are multifactorial, involving abnormal protein aggregation, impaired proteostasis, mitochondrial dysfunction, excitotoxicity, oxidative stress, and neuroinflammatory cascades [3,4]. Despite extensive research, current pharmacotherapy remains largely symptomatic cholinesterase inhibitors in AD, levodopa and dopamine agonists in PD, and riluzole in ALS—offering only temporary relief without altering disease progression [5,6].

Neuropharmacology bridges the understanding between molecular pathology and therapeutic modulation of neuronal activity. It explores how drugs act on CNS receptors, ion channels, transporters, and signaling cascades to restore or modify neural function [7]. In NDs, neuropharmacological research underpins target discovery, screening methodologies, and drug development pipelines [8].

Animal models and behavioral screening techniques play a critical role in evaluating efficacy and mechanistic validity prior to human clinical trials [9]. Parallel advances in biotechnology—particularly gene therapy, antisense oligonucleotides (ASOs), CRISPR/Cas9 genome editing, monoclonal antibodies, and stem cell therapy have initiated a new era of disease-modifying approaches [10–12].

This review integrates classical neuropharmacological concepts with modern therapeutic innovations, emphasizing preclinical screening methodologies, translational challenges, and future perspectives in the treatment of neurodegenerative disorders.

2. Neuropharmacological Basis of Neurodegeneration

2.1. Neurotransmitter systems and synaptic dysregulation

Neurodegeneration disrupts the delicate balance of neurotransmission across multiple systems. In AD, cholinergic deficits in the basal forebrain contribute to memory impairment [13]. PD involves dopaminergic neuron loss in the substantia nigra pars compacta, leading to striatal dopamine depletion and motor symptoms [14]. Glutamatergic excitotoxicity, mediated via NMDA receptor overactivation, causes neuronal calcium overload and cell death, observed in ALS and HD models [15].

Neuropharmacological interventions aim to restore neurotransmitter balance:

- Cholinesterase inhibitors (donepezil, rivastigmine) enhance cholinergic transmission [16].
- Dopaminergic agents (levodopa, pramipexole, MAO-B inhibitors) replenish dopamine in PD [17].

- NMDA receptor antagonists (memantine) mitigate excitotoxicity in AD [18].

Emerging strategies target receptor subtypes (mGluR5 antagonists, 5-HT1A agonists, adenosine A2A antagonists) to refine efficacy and limit side effects [19].

2.2. Mitochondrial dysfunction and oxidative stress

Mitochondrial damage and reactive oxygen species (ROS) accumulation are common denominators in NDs [20]. Complex I deficiency in PD and oxidative injury in AD correlate with impaired ATP production and apoptotic signaling [21]. Neuroprotective compounds such as coenzyme Q10, edaravone, and mitochondria-targeted antioxidants (MitoQ, SkQ1) are being evaluated for their ability to restore bioenergetic homeostasis [22]. Antioxidant defenses (superoxide dismutase, catalase, glutathione peroxidase) are frequently overwhelmed, justifying pharmacological strategies to enhance endogenous antioxidant capacity or inhibit ROS generation [23].

2.3. Protein aggregation and proteostasis imbalance

Misfolded proteins such as β-amyloid and tau in AD, α-synuclein in PD, and mutant huntingtin in HD form insoluble aggregates that disrupt neuronal function [24]. Molecular chaperones and the ubiquitin–proteasome system maintain proteostasis; their dysfunction accelerates pathology [25].

Small-molecule aggregation inhibitors, proteasome activators, and autophagy inducers (rapamycin, trehalose) are under investigation to enhance clearance of pathological proteins [26]. Monoclonal antibodies such as aducanumab and donanemab specifically target amyloid species to promote immunological removal, though clinical efficacy remains debated [27].

2.4. Neuroinflammation and glial activation

Chronic activation of microglia and astrocytes contributes to neuronal loss via release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) [28]. NF-κB signaling and NLRP3 inflammasome activation are pivotal in sustaining this inflammatory milieu [29].

Neuropharmacological modulation includes inhibitors of microglial activation (minocycline), selective COX-2 inhibitors, and modulators of cannabinoid or purinergic receptors (CB2 agonists, P2X7 antagonists) [30,31]. Recent research explores microglia-specific gene reprogramming to shift toward a neuroprotective phenotype [32].

2.5. Genetic factors and epigenetic modulation

Mutations in genes such as *APP*, *PSEN1/2*, *SNCA*, *LRRK2*, *HTT*, *SOD1*, *TARDBP*, and *C9orf72* predispose to familial forms of NDs [33]. Epigenetic alterations (DNA methylation, histone acetylation, noncoding RNAs) further regulate disease onset and progression [34]. Pharmacological epigenetic modulators histone deacetylase (HDAC) inhibitors, DNA methyltransferase inhibitors, and microRNA mimics represent an emerging therapeutic class

[35].These multi-layered mechanisms define the complex neuropharmacological landscape that guides screening strategies and therapeutic innovation.

3. Preclinical Screening in Neuropharmacology

3.1. Purpose and design principles

Preclinical screening serves as a bridge between molecular discovery and human trials. It evaluates pharmacodynamics, safety, and efficacy across in vitro and in vivo systems [36]. Successful translation demands model validity, reproducibility, appropriate controls, and statistically robust analysis [37].

The typical screening pipeline involves:

1. *In vitro* receptor binding and cell viability assays.
2. Pharmacokinetic profiling and BBB permeability assessment.
3. *In vivo* efficacy testing in validated animal models.
4. Correlation with molecular biomarkers and histological outcomes [38].

3.2. In vitro neuropharmacological assays

In vitro systems offer rapid, cost-effective insights into mechanism and toxicity. Examples include:

- Cellular toxicity assays: MTT, LDH release, and caspase activation in neuronal cell lines or induced pluripotent stem cell (iPSC) derived neurons [39].
- Receptor binding assays: Radioligand or fluorescence-based quantification of ligand–receptor affinity and selectivity [40].
- Electrophysiological recordings: Patch-clamp and multi-electrode arrays assess ion channel modulation by neuroactive compounds [41].
- Organotypic slice cultures and brain organoids: Enable evaluation of synaptic connectivity, electrophysiology, and neuroinflammation in human-relevant architectures [42].

Table 1. Major Neuropharmacological Targets Implicated in Neurodegenerative Diseases

Target System / Receptor	Function / Role	Pathological Implication	Therapeutic Modulators / Drugs
Cholinergic (Muscarinic, Nicotinic)	Cognitive processing, memory	Impaired in Alzheimer's disease (AD)	Donepezil, Rivastigmine, Galantamine
Dopaminergic (D1–D5)	Motor control, reward	Degeneration of nigrostriatal neurons in Parkinson's disease (PD)	Levodopa, Ropinirole, Pramipexole

GABAergic	Inhibitory neurotransmission	Loss of inhibitory tone → excitotoxicity	Benzodiazepines, Tiagabine
Glutamatergic (NMDA, AMPA)	Learning and synaptic plasticity	Overactivation causes excitotoxic neuronal death	Memantine, Riluzole
Serotonergic (5-HT1A, 5-HT2A)	Mood regulation, cognition	Dysregulated in depression, PD	SSRIs, Buspirone
Adrenergic (α, β receptors)	Arousal, stress response	Imbalance linked to anxiety, cognitive decline	Propranolol, Atomoxetine
Histaminergic (H3 receptors)	Modulates arousal, cognition	Altered histamine tone in AD	Pitolisant
Endocannabinoid (CB1/CB2)	Neuroprotection, inflammation control	Altered signaling in AD, MS	Cannabidiol, CB2 agonists
Adenosinergic (A2A)	Neuroinflammation modulation	Overactivation in PD	Istradefylline

3.3. In vivo behavioral screening

Behavioral paradigms translate neurochemical modulation into observable outcomes of motor, cognitive, and emotional function [43].

3.3.1. Motor coordination and balance

- Rotarod test: Measures latency to fall from a rotating rod, evaluating cerebellar and basal ganglia function; widely applied in PD and HD models [44].
- Open field test: Quantifies spontaneous locomotion, exploratory behavior, and anxiety-like responses [45].
- Grip strength and beam walk: Assess neuromuscular integrity, crucial for ALS and SMA studies [46].

3.3.2. Learning and memory

- Morris water maze (MWM): Gold standard for spatial learning; sensitive to hippocampal dysfunction [47].
- Novel object recognition (NOR): Evaluates recognition memory using innate exploratory preference.
- Y-maze/T-maze alternation: Tests working memory via spontaneous alternation behavior [48].

3.3.3. Anxiety and affective behaviour

- Elevated plus maze (EPM): Measures anxiety via open vs. closed arm exploration.

- Forced swim and tail suspension tests: Indicate depressive-like behavior and screen antidepressant potential [49].

3.3.4. Disease-specific paradigms

- Apomorphine-induced rotations: Quantifies dopaminergic imbalance after unilateral 6-OHDA lesions in PD models [44].
- Gait analysis: Monitors fine motor control and coordination deficits.
- Three-chamber social interaction test: Evaluates social behavior, relevant to frontotemporal dementia and autism-linked neurodegeneration [50].

Behavioral data should be analyzed by blinded observers with automated tracking systems, using appropriate statistical tools to ensure reliability.

4. Animal Models in Neurodegenerative Research

Animal models replicate key pathological and behavioral features of human neurodegenerative diseases (NDs), offering indispensable tools for preclinical neuropharmacological evaluation [51]. These models are broadly classified into neurotoxin-induced, transgenic/genetic, and lesion-based paradigms.

4.1. Alzheimer's disease (AD) models

- Chemical models: Administration of scopolamine impairs cholinergic transmission and induces transient cognitive deficits [52]. Streptozotocin (STZ) intracerebroventricular injection generates insulin-resistant brain states mimicking sporadic AD [53].
- Transgenic models: *APP/PS1*, *3xTg-AD*, and *Tg2576* mice overexpress mutant amyloid precursor protein (APP) and presenilin genes, leading to amyloid plaque deposition and tau pathology [54]. Behavioral deficits (memory loss, anxiety) and biochemical markers (Aβ1–42, tau hyperphosphorylation) correlate strongly with human pathology [55].

4.2. Parkinson's disease (PD) models

- Neurotoxin-induced: 6-hydroxydopamine (6-OHDA) lesions selectively destroy nigrostriatal dopaminergic neurons, producing unilateral rotational behavior [56]. MPTP administration reproduces mitochondrial complex I inhibition and dopaminergic cell loss [57].
- Genetic models: *SNCA* and *LRRK2* transgenic mice demonstrate progressive α-synuclein accumulation and Lewy body-like pathology [58]. These models facilitate assessment of dopaminergic neuroprotectants, anti-inflammatory agents, and gene therapies.

4.3. Huntington's disease (HD) models

- Toxin-based models: Quinolinic acid or 3-nitropropionic acid induce selective striatal degeneration [59].
- Transgenic models: *R6/2* and *YAC128* mice express mutant huntingtin (mHTT) with expanded CAG repeats, displaying motor impairment and cognitive decline [60]. Screening focuses on mHTT aggregation inhibitors, mitochondrial protectants, and gene-silencing therapies.

4.4. Amyotrophic lateral sclerosis (ALS) and other motor neuron disease models

The *SOD1-G93A* mouse model exhibits progressive motor weakness, axonal degeneration, and glutamate excitotoxicity resembling human ALS [61].
Emerging models utilize *TARDBP* and *FUS* mutations for frontotemporal-ALS spectrum studies [62].

4.5. Validation and translational value

While these models recapitulate individual disease aspects, none fully reproduces human complexity [63]. Hence, neuropharmacological screening relies on a combination of genetic and environmental models, supported by histopathology, neurochemical analysis, and advanced imaging (PET/MRI) [64].

5. Advanced Therapeutic Strategies in Neurodegenerative Diseases

Rapid advances in molecular neuroscience and biotechnology have revolutionized neurotherapeutic design, transitioning from symptomatic to disease-modifying strategies.

Table 2. Commonly Used Animal Models for Neurodegenerative Disease Screening

Disease	Experimental Model / Induction Method	Behavioral / Biochemical Assessment	Key Applications
Alzheimer's Disease (AD)	Scopolamine-induced amnesia, Transgenic APP/PS1 mice	Morris water maze, Y-maze, AChE activity, β-amyloid quantification	Screening of memory enhancers, anti-amyloid agents
Parkinson's Disease (PD)	6-OHDA or MPTP lesion models	Rotarod, open-field, dopamine assay	Dopaminergic neuroprotection screening
Huntington's Disease (HD)	3-Nitropropionic acid (3-NP), R6/2 transgenic mice	Motor coordination, striatal degeneration	Glutamate antagonists, mitochondrial stabilizers

Amyotrophic Lateral Sclerosis (ALS)	SOD1-G93A transgenic mice	Grip strength, survival curve, motor neuron histology	Neuroprotective and anti-inflammatory agents
Multiple Sclerosis (MS)	Experimental autoimmune encephalomyelitis (EAE)	Clinical scoring, cytokine assay, myelin staining	Immunomodulators, neuroprotective drugs

5.1. Gene therapy

Gene therapy introduces or corrects genetic information using viral or nonviral vectors. **Adeno-associated viruses (AAVs)** are widely used due to their neuronal tropism and safety profile [65].

- In PD, AAV-mediated delivery of aromatic L-amino acid decarboxylase (AADC) enhances dopamine synthesis [66].
- In SMA, *onasemnogene abeparvovec* (Zolgensma®) delivers a functional *SMN1* gene, dramatically improving survival [67].
- CRISPR-Cas9 editing allows precise correction of pathogenic mutations in *SOD1* (ALS) and *HTT* (HD) [68].

5.2. Antisense oligonucleotides (ASOs)

ASOs are short, synthetic nucleic acid sequences that modulate RNA expression through degradation or splicing correction [69].

- *Nusinersen* (Spinraza®) for SMA and *tofersen* for *SOD1*-ALS exemplify clinically approved ASO therapies [70].
- Preclinical trials show promise in reducing mutant huntingtin and tau mRNA levels [71].

Chemical modifications (2′-O-methoxyethyl, phosphorothioate backbones) enhance ASO stability and CNS penetration [72].

5.3. Stem cell and regenerative therapy

Stem cell-based interventions aim to replace lost neurons and restore synaptic circuits [73]. **Embryonic stem cells (ESCs)** and **induced pluripotent stem cells (iPSCs)** differentiate into dopaminergic or cholinergic neurons [74]. Transplantation of iPSC-derived dopaminergic neurons into PD models improves motor function and dopamine release [75]. Challenges include immune rejection, tumorigenesis, and integration efficacy [76].

5.4. Immunotherapy and monoclonal antibodies

- **Passive immunization** employs monoclonal antibodies to clear pathological proteins. *Aducanumab* and *donanemab* target Aβ aggregates, while *prasinezumab* targets α-synuclein [77].
- **Active immunization** (vaccination) stimulates endogenous antibody production but carries risks of neuroinflammation [78].
- Recent bispecific antibodies target multiple epitopes, improving clearance efficiency [79].

5.5. Small molecules and repurposed drugs

Neuroprotective small molecules remain vital for affordability and oral delivery. Examples include **ambroxol** (glucocerebrosidase activator in PD), **nilotinib** (autophagy inducer), and **metformin** (AMPK activator with neuroprotective effects) [80,81].
Drug repurposing accelerates clinical translation by leveraging established pharmacokinetics [82].

5.6. Neuromodulation and brain-targeted delivery

- Deep brain stimulation (DBS) of the subthalamic nucleus or globus pallidus alleviates motor symptoms in PD [83].
- Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) modulate cortical excitability and plasticity in depression and AD [84].
- Focused ultrasound (FUS) with microbubbles transiently opens the blood brain barrier (BBB), enabling targeted delivery of drugs, genes, or antibodies [85].

Table 3. Advanced Molecular and Cellular Approaches in Neurodegenerative Therapy

Therapeutic Strategy	Mechanism of Action	Current Research / Example	Clinical Status
Gene Therapy	Delivery of functional genes to replace defective ones	AAV2-GDNF for PD; AAV9-SMN1 for ALS	Several in phase II/III trials
Stem Cell Therapy	Replacement of degenerated neurons	iPSC-derived dopaminergic neurons	Early clinical trials
CRISPR/Cas9 Genome Editing	Correction of disease-causing mutations	Targeting HTT gene in HD	Preclinical
Nanoparticle-Mediated Drug Delivery	Enhanced BBB penetration and sustained release	Liposomal curcumin, polymeric nanoparticles	Preclinical to phase I
Neurotrophic Factor Therapy	Enhancement of neuronal survival	BDNF, NGF, GDNF administration	Clinical evaluation
Immunotherapy (Active/Passive)	Clearance of toxic protein aggregates	Anti-Aβ monoclonal antibodies (Aducanumab)	Approved for AD
Mitochondrial Protective Agents	Prevention of oxidative stress	Coenzyme Q10, MitoQ, nicotinamide riboside	Clinical trials
RNA-Based Therapy (siRNA, ASO)	Silencing of mutant genes	Tofersen for SOD1-ALS	FDA approved (2023)

6. Translational Challenges and Regulatory Considerations

Despite remarkable preclinical success, translation of neuropharmacological findings into effective therapies remains difficult.

6.1. Blood–brain barrier (BBB)

The BBB restricts entry of most large molecules and hydrophilic drugs. Nanocarriers, exosomes, and receptor-mediated transcytosis systems (transferrin, insulin, or LRP1 ligands) are being explored to enhance CNS delivery [86].

6.2. Biomarker limitations

Reliable biomarkers for disease progression and treatment response are lacking. Advances in cerebrospinal fluid (CSF) proteomics, neurofilament light chain (NfL) quantification, and PET tracers for tau/α-synuclein are promising but not universally validated [87].

6.3. Model–human divergence

Rodent models often fail to replicate human disease complexity and timescales [88]. Human iPSC-derived neurons and organoids now serve as adjunct platforms bridging the translational gap [89].

6.4. Ethical and regulatory framework

Gene and stem cell therapies pose unique ethical challenges. Regulatory agencies (FDA, EMA) mandate long-term safety and post-marketing surveillance [90]. Ethical consent, off-target analysis, and equitable access remain paramount [91].

Table 4. Comparative Overview of Conventional and Emerging Drug Therapies

Category	Example Drugs / Agents	Mechanistic Target	Therapeutic Limitations
Cholinesterase Inhibitors	Donepezil, Rivastigmine	AChE inhibition → ↑ ACh	Symptomatic relief only
NMDA Receptor Antagonists	Memantine	Inhibition of excitotoxic glutamate signaling	Limited cognitive benefit
Dopamine Precursors / Agonists	Levodopa, Pramipexole	Restores dopaminergic tone	Motor fluctuations, dyskinesia
Neuroprotective Agents	Selegiline, Riluzole	Reduces oxidative stress	Partial efficacy
Monoclonal Antibodies	Aducanumab, Lecanemab	Amyloid clearance	Controversial efficacy, high cost
Stem Cell Therapies	hESCs, iPSCs	Cell replacement	Ethical and safety concerns
Gene / RNA Therapies	AAV, ASO platforms	Genetic correction	Delivery and immune response issues
Nanomedicine Approaches	Polymeric/lipid nanoparticles	Targeted brain delivery	Regulatory challenges

7. Future Perspectives

The convergence of **neuropharmacology, genomics, and precision medicine** is transforming ND research. Artificial intelligence (AI) accelerates drug discovery via predictive modeling of ligand–target interactions [92]. Multi-omics integration genomics, transcriptomics, proteomics, metabolomics—enables personalized treatment design [93]. Combination therapies, integrating neuroprotective small molecules with gene or cell-based interventions, are expected to yield synergistic benefits [94].

Non-invasive neuromodulation, nanotechnology-driven delivery, and closed-loop DBS systems further promise individualized therapy with real-time feedback [95].Ultimately, collaborative translational frameworks uniting academic, clinical, and regulatory sectors will be essential for clinical success [96].

8. Conclusions

Neuropharmacology has evolved from receptor pharmacodynamics to a systems-level understanding of neuronal survival, signaling, and plasticity. Preclinical screening models, though imperfect, remain vital in deciphering molecular pathophysiology and assessing candidate therapeutics. The integration of gene therapy, ASOs, stem cell transplantation, and neuromodulation defines a new era of disease-modifying interventions for neurodegenerative disorders. Future progress will depend on overcoming BBB barriers, refining biomarkers, and ensuring ethical, equitable access to innovative therapies. As neuropharmacology embraces personalized and regenerative paradigms, the prospect of genuine neurorestoration becomes increasingly attainable.

Conflict of interest: None

Acknowledgement: None to acknowledge

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