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NEUROPHARMACOLOGICAL APPROACHES TO THE TREATMENT OF NEURODEGENERATIVE DISORDERS

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Abstract

Neurodegenerative disorders are characterized by progressive dysfunction and loss of selectively vulnerable neuronal populations, yet their molecular drivers extend beyond neuronal death to include protein misfolding, synaptic failure, mitochondrial dysfunction, excitotoxicity, impaired proteostasis, neuroinflammation and disruption of brain-barrier homeostasis. The objective of this structured review was to evaluate contemporary neuropharmacological approaches for Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis and related disorders, with emphasis on the transition from symptomatic neurotransmitter replacement toward disease-modifying and precision strategies. International literature published predominantly between 2020 and 2025 was synthesized using an IMRAD-oriented framework. Current symptomatic therapies remain clinically important: cholinesterase inhibitors and memantine are used in Alzheimer disease, while levodopa and adjunct dopaminergic agents remain central to Parkinson disease. However, recent clinical evidence supports disease-modifying potential in selected populations through anti-amyloid monoclonal antibodies, and target-specific RNA therapy has established a mechanistic precedent in SOD1-associated amyotrophic lateral sclerosis. Emerging approaches include tau- and α-synuclein-directed interventions, microglial and immune modulation, synapse-protective pharmacology, gene therapy, antisense oligonucleotides and engineered delivery systems that improve central nervous system exposure. The major future challenge is to match mechanism, disease stage, molecular phenotype and delivery technology while maintaining an acceptable benefit-risk profile. Precision neuropharmacology is therefore expected to integrate biomarkers, genetics and adaptive treatment monitoring rather than rely on a single disease-wide pharmacological strategy.

Keywords: neuropharmacology; neurodegeneration; Alzheimer disease; Parkinson disease; amyotrophic lateral sclerosis; neuroinflammation; antisense oligonucleotides; gene therapy; blood-brain barrier.

1. INTRODUCTION

Neurodegenerative disorders represent a heterogeneous group of chronic diseases in which progressive molecular and cellular dysfunction eventually produces cognitive, behavioral or motor disability. Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD) and amyotrophic lateral sclerosis (ALS) differ in their dominant clinical phenotypes, but they share several convergent mechanisms, including abnormal protein handling, oxidative and mitochondrial stress, altered neurotransmission, synaptic

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loss, neuroimmune activation and selective neuronal vulnerability (1,8,9). This convergence is pharmacologically important because it creates both disease-specific targets and cross-disease targets that can be approached with small molecules, biologics, nucleic-acid therapeutics and advanced delivery systems.

For decades, neuropharmacology was dominated by symptomatic correction of neurotransmitter deficits. In AD, acetylcholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine are used to improve or stabilize symptoms in selected patients. In PD, levodopa remains the most effective pharmacological treatment of motor manifestations, with dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, amantadine and other agents used according to disease stage and complication profile (1,4). These therapies have major clinical value, but they do not fully address the molecular processes that drive continuing neurodegeneration.

The therapeutic landscape is now changing. Anti-amyloid monoclonal antibodies have demonstrated that a pathology-directed intervention can modify biomarker burden and slow clinical decline in carefully selected patients with early AD, although treatment is accompanied by clinically relevant safety and implementation requirements (2,3). In genetically defined ALS, the antisense oligonucleotide (ASO) tofersen lowers SOD1 and neurofilament biomarkers and provides a prototype for target-specific RNA therapeutics (5). At the same time, tau, α-synuclein, microglial states, immune signaling, synapse biology and blood-brain barrier (BBB) transport are increasingly investigated as pharmacological intervention points (6-10,13-15).

The aim of this article is to synthesize current and emerging neuropharmacological approaches to neurodegenerative disorders, compare their mechanisms and translational limitations, and define the major principles likely to shape future disease-modifying therapy. Particular attention is given to pharmacodynamic target engagement, CNS delivery, biomarker-guided selection and treatment safety.

2. MATERIALS AND METHODS

A structured narrative review design was used. International peer-reviewed literature was identified from PubMed-indexed and major clinical-journal sources, with priority given to publications from 2020-2025 and to pivotal randomized trials, contemporary clinical guidelines and high-level mechanistic reviews. Search concepts included “neurodegenerative disease pharmacotherapy,” “Alzheimer anti-amyloid,” “Parkinson pharmacotherapy,” “SOD1 ALS tofersen,” “tau therapeutics,” “alpha-synuclein therapeutics,” “microglia neurodegeneration,” “synapse neuroprotection,” “gene therapy CNS,” “antisense oligonucleotide neurological disease,” and “blood-brain barrier drug delivery.” Older sources were considered only when needed to establish a pharmacological principle.

Eligible evidence was grouped into five domains: (1) symptomatic neurotransmitter-based pharmacotherapy; (2) pathology-directed biologics; (3) gene and RNA therapeutics; (4) neuroimmune and synapse-directed strategies; and (5) CNS delivery technologies. For each domain, mechanism of action, representative drug or platform, principal therapeutic objective, major limitation and level of clinical maturity were extracted. Because this

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article is a literature synthesis rather than an original interventional study, no patient-level data were generated and no fabricated experimental outcomes were introduced. Findings were integrated qualitatively and organized to show the transition from symptom control to mechanism-based precision neuropharmacology.

3. RESULTS

The evidence indicates that modern neuropharmacology can be viewed as a layered therapeutic system. The first layer restores or modulates neurotransmission and remains essential for symptom control. The second layer attempts to modify disease biology by reducing toxic protein species or altering downstream pathological cascades. The third layer uses genetic or molecular stratification to target a defined mechanism, while the fourth addresses the delivery problem created by the BBB and cell-type specificity. These layers are complementary rather than mutually exclusive.

Table 1. Current and emerging neuropharmacological approaches across major neurodegenerative disorders

Disorder / domain	Representative approach	Primary mechanism	Clinical role / evidence	Key limitation
AD	Cholinesterase inhibitors; memantine	Enhance cholinergic signaling or reduce pathological NMDA-mediated excitatory drive	Symptomatic cognitive/functional benefit in selected patients (1)	No established reversal of underlying neurodegeneration
Early AD	Lecanemab; donanemab	Antibody-mediated removal of aggregated Aβ species	Slower clinical decline with amyloid reduction in pivotal trials (2,3)	ARIA, infusion burden, patient selection and monitoring
PD	Levodopa ± MAO-B/COMT inhibitors, dopamine agonists	Restore or prolong dopaminergic signaling	Core treatment of motor symptoms across disease stages (4)	Fluctuations, dyskinesia and non-motor progression
SOD1-ALS	Tofersen ASO	Reduces SOD1 mRNA/protein expression	Target engagement and biomarker reduction; genotype-specific therapy (5)	Restricted to SOD1-ALS; intrathecal delivery

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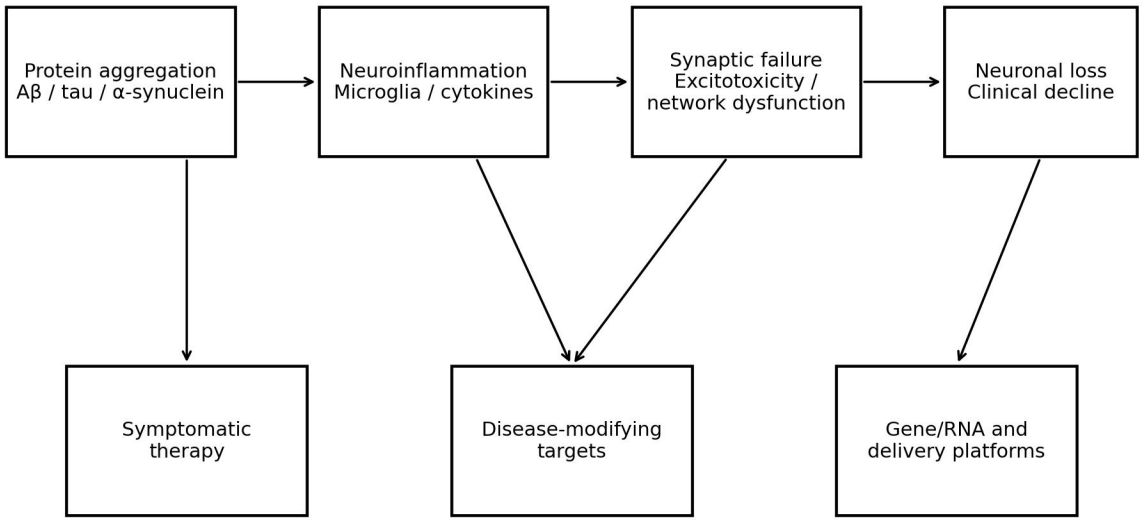
AD / tauopathies	Tau-directed immunotherapy or ASO strategies	Reduce tau expression, aggregation or propagation	Multiple clinical-stage programs; efficacy still under evaluation (6)	Target/epitope selection, timing and brain exposure
PD / synucleinopathies	α-synuclein-directed therapies	Reduce synthesis, aggregation, spread or enhance clearance	Strong mechanistic rationale; ongoing translational development (7)	Heterogeneous pathology and uncertain optimal target species
Cross-disease	Microglial / immune modulation	Shift maladaptive neuroimmune signaling toward protective states	Expanding target portfolio across AD, PD and ALS (8,10)	Context-dependent immune functions and safety
Cross-disease	Synapse-protective approaches	Preserve synaptic integrity and network function	Emerging disease-agnostic target class (9)	Need validated pharmacodynamic biomarkers

The best-established disease-modifying clinical evidence is currently concentrated in early AD. In the phase 3 Clarity AD trial, lecanemab produced greater amyloid removal and less worsening on clinical measures than placebo over 18 months, while amyloid-related imaging abnormalities (ARIA) and infusion reactions remained important safety considerations (2). Donanemab likewise slowed clinical progression in early symptomatic AD with amyloid and tau pathology, but treatment was associated with ARIA and requires careful imaging and risk management (3). These studies demonstrate a central neuropharmacological principle: molecular target engagement may translate into measurable clinical benefit, but effect size, disease stage and toxicity determine real-world therapeutic value.

In PD, contemporary guidelines confirm that levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors and other established agents should be selected according to age, symptom pattern, treatment response and complication risk (4). This remains predominantly symptomatic pharmacology. In parallel, disease-modifying research has shifted toward α-synuclein aggregation and clearance, lysosomal biology, mitochondrial stress and genetically defined pathways. The α-synuclein field illustrates the difficulty of target selection because different conformers, intracellular and extracellular pools, and disease-specific strains may have distinct biological effects (7).

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Figure 1. Major neurodegenerative mechanisms and neuropharmacological intervention points



The diagram shows that symptomatic and disease-modifying interventions act at different levels of the same pathological cascade.

ALS provides an especially clear example of precision neuropharmacology. Tofersen is an ASO designed to reduce SOD1 synthesis in patients with pathogenic SOD1 variants. In the pivotal randomized trial, tofersen substantially reduced CSF SOD1 and plasma neurofilament light concentrations, whereas the prespecified 28-week clinical primary endpoint did not show a statistically significant difference; open-label extension data supported the importance of treatment timing and longer observation (5). The main conceptual advance is that neurodegenerative pharmacotherapy can be linked directly to a molecular genotype and a measurable target-engagement biomarker.

Across diseases, microglia and immune signaling are increasingly recognized as active pharmacological systems rather than passive consequences of neuronal injury. Microglia can clear pathological protein aggregates and support tissue homeostasis, but chronic or maladaptive states can amplify cytokine signaling, synaptic injury and propagation of pathogenic proteins (8,10). Consequently, therapeutic strategies include modulation of microglial phenotype, inflammasome pathways, complement signaling, regulatory T-cell responses and other immune interfaces. The challenge is to avoid indiscriminate immunosuppression because neuroimmune responses can be protective or harmful depending on disease stage and cellular state.

Synaptic dysfunction is another convergent therapeutic domain. Synapse loss correlates closely with functional decline in several neurodegenerative disorders, and emerging approaches aim to preserve synaptic proteins, reduce complement-mediated synapse elimination, normalize network excitability and enhance plasticity (9). This strategy may

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complement protein-targeting therapies because neuronal function can deteriorate before extensive cell death is present.

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Table 2. Translational priorities for next-generation neuropharmacology

Priority	Pharmacological rationale	Representative technologies	Main translational question
Molecular stratification	Match treatment to dominant disease mechanism or genotype	Amyloid/tau biomarkers, SOD1 and other genetic testing, molecular imaging	Which patients have the target that the drug actually modifies?
Earlier intervention	Treat before irreversible neuronal loss dominates	Prodromal biomarkers, blood/CSF markers, risk-enriched cohorts	How early is biologically necessary and clinically acceptable?
CNS delivery	Increase target-site exposure while limiting systemic toxicity	AAV vectors, ASOs, nanoparticles, receptor-mediated BBB transport (11-15)	Can sufficient drug reach the correct region and cell type safely?
Pharmacodynamic monitoring	Demonstrate target engagement during treatment	Amyloid PET, neurofilament, CSF proteins, digital functional measures	Does biomarker change predict durable clinical benefit?
Combination therapy	Address multiple interacting mechanisms	Protein-targeting + immune/synaptic/metabolic strategies	Which combinations add benefit without additive toxicity?

4. DISCUSSION

The principal finding of this review is that neuropharmacology is moving from a neurotransmitter-centric model toward a multi-level precision framework. Symptomatic drugs remain indispensable because they directly improve clinically meaningful functions, and the arrival of disease-modifying strategies does not eliminate the need for them. Instead, future treatment is likely to combine symptomatic optimization with molecularly targeted therapy in patients selected by disease stage, biomarker profile and genotype.

AD illustrates both the promise and the complexity of this transition. Lecanemab and donanemab provide proof that substantial reduction of amyloid pathology can be accompanied by slower decline in early disease (2,3). However, these therapies also show why neuropharmacological success cannot be judged only by target engagement. MRI monitoring, ARIA risk, infusion logistics, comorbidity, anticoagulant exposure and patient preference all influence the benefit-risk assessment. Furthermore, amyloid removal does not directly address tau pathology, synaptic dysfunction, inflammation and vascular contributions. Combination or sequential strategies may therefore become necessary as the field matures (6,8-10).

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In PD, the therapeutic gap is different. Dopaminergic pharmacology is highly effective for motor symptoms but does not reliably prevent the progressive loss of nigrostriatal and extra-nigral function. Disease-modifying programs directed at α-synuclein must solve several unresolved problems: which molecular species is toxic, where in the disease course the intervention should begin, how to demonstrate target engagement in the living brain, and whether reduction of extracellular or intracellular α-synuclein is sufficient (7). Similar questions apply to tau therapies in AD and primary tauopathies (6).

Gene and RNA therapeutics expand the pharmacological toolkit by allowing the drug target itself to be genetically regulated. ASOs can reduce production of a pathogenic protein without requiring a conventional enzyme or receptor binding pocket, while AAV platforms can provide durable expression of a therapeutic gene (5,11,12). Their major limitations are delivery, immunogenicity, dose control, durability, reversibility and manufacturing complexity. In the CNS, route of administration is particularly important because intrathecal, intracisternal, intraparenchymal and systemic approaches generate very different biodistribution profiles. Modern gene-therapy development therefore requires integration of vector pharmacology with neuroanatomy and immune safety (11,12).

The BBB remains one of the central reasons why promising neuropharmacological candidates fail to translate. It protects the CNS by tightly regulating molecular transport, but the same selectivity restricts exposure of antibodies, nucleic acids and many small molecules. Disease-associated BBB dysfunction does not automatically improve useful delivery because barrier breakdown can be regionally heterogeneous and may worsen neuroinflammation (13). Engineered nanoparticles, receptor-mediated transport, focused delivery strategies and optimized viral vectors aim to increase brain exposure and cell-type precision (14,15). A successful CNS therapy must therefore satisfy two pharmacological requirements simultaneously: the molecule must act on the correct target and it must reach that target at an effective, tolerable concentration.

Another major trend is the use of biomarkers as pharmacodynamic tools. Classical neurology relied heavily on clinical rating scales, which may change slowly and can be influenced by symptomatic treatment. Molecular imaging, CSF proteins, plasma neurofilament, phosphorylated tau species, seed-amplification assays and digital functional endpoints can provide earlier evidence of biological activity. The tofersen program demonstrates the value and the limitation of this approach: strong biomarker effects can establish target engagement, but clinical benefit may require longer follow-up or earlier treatment (5). Biomarkers should therefore complement, not replace, patient-centered clinical outcomes.

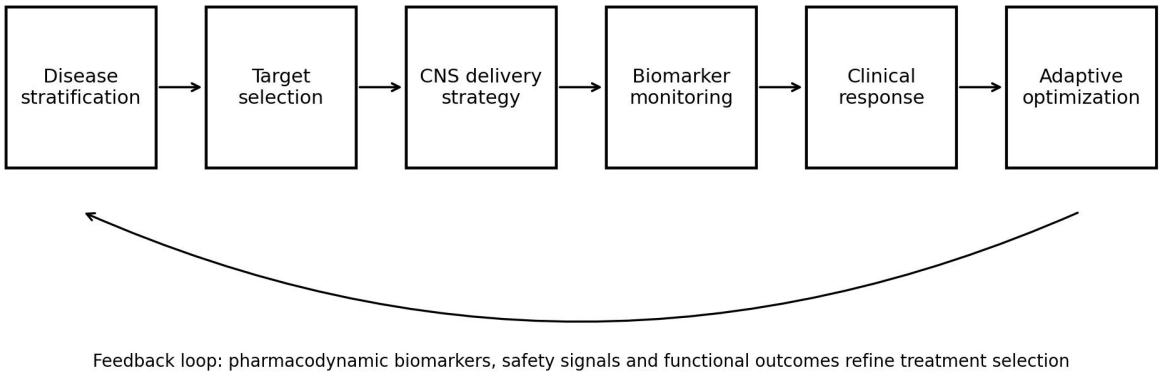
The future is also likely to be combinatorial. Neurodegeneration is not a single linear pathway; protein aggregation, inflammation, mitochondrial stress, axonal dysfunction, synapse loss and vascular abnormalities interact in feedback loops. A single agent may be sufficient when one dominant genetically defined mechanism drives disease, but sporadic disorders may require combination therapy or stage-specific sequencing. Such regimens will need careful pharmacokinetic and pharmacodynamic design to avoid overlapping neurotoxicity or systemic adverse effects.

This review has limitations. It was structured as a narrative synthesis rather than a formal meta-analysis, and the evidence base is uneven across diseases. AD currently has

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more advanced pathology-directed clinical trial data than many other neurodegenerative disorders. Emerging approaches such as α-synuclein immunotherapy, tau ASOs, microglial modulation and advanced delivery systems remain at different stages of clinical validation. Accordingly, mechanistic plausibility should not be interpreted as established clinical efficacy.

Figure 2. Precision neuropharmacology workflow for future disease-modifying treatment



The future model links molecular diagnosis, target-specific therapy, CNS delivery and iterative biomarker monitoring.

5. CONCLUSION

Contemporary neuropharmacology is undergoing a transition from symptom-centered treatment toward disease-modifying and precision strategies. Established neurotransmitter-based therapies remain essential, particularly dopaminergic therapy in PD and cholinergic/NMDA-directed treatment in AD. At the same time, anti-amyloid antibodies have established clinically measurable pathology-directed treatment in early AD, while tofersen has demonstrated the feasibility of genotype-specific RNA therapy in SOD1-ALS. Tau, α-synuclein, microglia, synapses and immune pathways represent major emerging targets. Gene therapy, ASOs and engineered CNS delivery systems broaden the range of druggable mechanisms but also introduce new safety and delivery challenges. Future therapeutic success will depend on matching the right target to the right patient at the right disease stage, confirming target engagement with biomarkers, and ensuring adequate CNS exposure with acceptable risk. The most realistic long-term model is therefore personalized, biomarker-guided and multimodal neuropharmacotherapy rather than a universal single-drug solution.

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