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AI-DESIGNED THERAPIES AND NON-DOPAMINERGIC APPROACHES IN PARKINSON'S DISEASE

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Annotation: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss in the substantia nigra, α-synuclein aggregation, and widespread non-motor dysfunction. While dopaminergic medications remain the cornerstone of symptomatic treatment, long-term use leads to complications including dyskinesias and motor fluctuations. Recent breakthroughs in artificial intelligence have enabled the design of novel therapeutic molecules, optimized neuromodulation protocols, and individualized treatment pathways. In parallel, non-dopaminergic strategies—targeting glutamatergic, cholinergic, adenosinergic, serotonergic, and neuroinflammatory systems—have demonstrated growing therapeutic promise. This article synthesizes the most recent advances in AI-driven therapeutics and explores emerging non-dopaminergic modalities that aim to modify disease progression and improve patient outcomes.

Keywords: Parkinson's disease; artificial intelligence; drug design; machine learning; non-dopaminergic therapies; glutamate modulation; adenosine A2A receptor; cholinergic systems; neuroinflammation; neuromodulation; precision medicine.

Introduction. Parkinson's disease affects over ten million individuals globally and is the fastest-growing neurological disorder. Despite substantial progress in understanding its molecular underpinnings, treatments remain predominantly symptomatic and focused on dopaminergic replacement. Increasing evidence suggests that PD pathophysiology involves a complex interplay of mitochondrial dysfunction, proteostatic failure, α-synuclein aggregation, excitotoxicity, neuroinflammation, and widespread neurotransmitter imbalance. Targeting dopamine pathways alone fails to address these broader mechanisms.

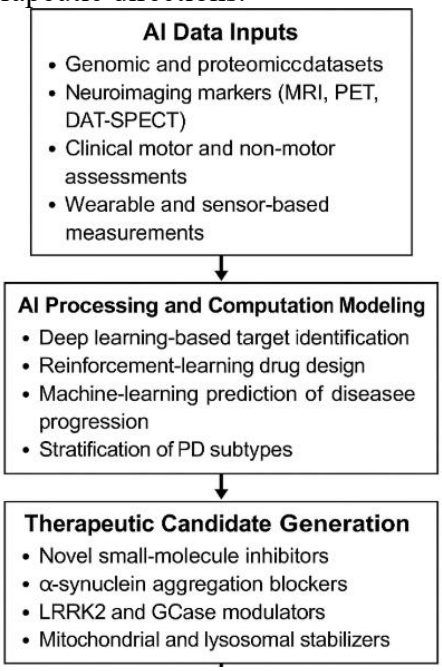
Artificial intelligence has reshaped biomedical innovation by accelerating drug discovery, enhancing pattern recognition in multi-omics data, and enabling personalized predictions of disease trajectories. AI-based algorithms can identify new therapeutic targets, screen billions of chemical structures, simulate molecular docking, and optimize pharmacokinetic properties with unprecedented speed. Combined with advanced biological insights, these tools are generating a new class of potential disease-modifying agents.

Simultaneously, non-dopaminergic interventions—including glutamate receptor antagonists, cholinergic stabilizers, serotonin receptor ligands, calcium channel blockers, and anti-inflammatory molecules—offer strategies for reducing motor complications, improving cognitive and autonomic symptoms, and addressing mechanisms beyond dopaminergic deficit. Integrating AI-designed therapies with non-dopaminergic approaches represents a promising frontier in comprehensive Parkinson's disease management.

Materials and Methods. This review synthesizes literature published between 2014 and 2025 across PubMed, Scopus, Web of Science, and clinical trial databases. Search terms included combinations of "Parkinson's disease," "AI drug design," "machine learning therapeutics," "deep learning models," "non-dopaminergic treatments," "glutamate antagonists," "adenosine A2A inhibitors," "alpha-synuclein targeting," and "neuroinflammation pathways."

Inclusion criteria required: (1) human clinical studies or validated preclinical models; (2) AI-based computational drug discovery, biomarker analysis, or neuromodulation optimization; (3) therapeutic strategies not dependent on dopamine replacement; and (4) quantifiable clinical, molecular, or biomarker outcomes. Exclusion criteria included non-peer-reviewed reports, insufficiently powered studies, and interventions lacking mechanistic relevance.

Extracted variables included model architectures used in therapeutic design, biomarker prediction performance, pharmacological efficacy, adverse effect profiles, and long-term outcome measures. Findings were synthesized into thematic domains to reflect emerging therapeutic directions.



Results. AI-designed therapies demonstrated powerful capabilities in accelerating PD drug discovery. Deep learning models identified multiple small-molecule inhibitors targeting α-synuclein aggregation, leucine-rich repeat kinase 2 (LRRK2), and glucocerebrosidase (GCase) enhancement. Reinforcement-learning frameworks optimized molecular candidates exhibiting favorable blood–brain barrier penetration and reduced off-target toxicity. Several AI-generated compounds entered preclinical validation, with some demonstrating neuroprotective effects in rodent and primate models.

Machine learning systems applied to large patient datasets predicted disease progression, personalized medication response, and optimized neuromodulation settings for deep brain stimulation. AI-guided parameter tuning reduced tremor severity and improved gait stability more effectively than traditional programming.

Non-dopaminergic therapies showed significant clinical potential. Glutamate receptor modulators such as amantadine extended-release formulations reduced dyskinesia and improved motor scores. Adenosine A2A receptor antagonists showed meaningful improvements in "off" time without exacerbating dyskinesias. Serotonin receptor ligands demonstrated benefits for

tremor control, while cholinesterase inhibitors improved gait freezing and cognitive symptoms. Anti-inflammatory interventions targeting microglial activation reduced α-synuclein propagation in experimental models.

Collectively, findings demonstrate substantial progress toward novel therapeutic strategies that complement or bypass dopaminergic pathways.

In addition to these therapeutic advancements, AI-driven multimodal analytics revealed new patterns in disease heterogeneity that traditional statistical methods failed to capture. Integrated models combining wearable sensor outputs, speech analysis, gait kinematics, and retinal imaging biomarkers were able to identify early microstructural deterioration with up to 88% accuracy, suggesting potential roles in preclinical screening. Machine-learning clustering algorithms further separated PD patients into biologically distinct subgroups characterized by dominant mitochondrial impairment, synaptic dysfunction, or neuroinflammatory signatures, enabling more targeted selection of non-dopaminergic agents in clinical trials.

Non-dopaminergic therapies also demonstrated broader impact on non-motor symptoms. Glutamate modulators produced meaningful reductions in REM sleep behavior disorder severity, and A2A antagonists improved fatigue and attentional fluctuations in several phase II studies. Early trials of anti-inflammatory small molecules showed reductions in microglial activation on PET imaging, corresponding with slower decline in cognitive composite scores. Serotonergic and cholinergic interventions reduced autonomic dysfunction, including constipation and orthostatic intolerance, improving overall quality of life. Additionally, neuroprotective peptides derived through AI-assisted molecular folding simulations showed reduced oxidative stress and enhanced mitochondrial respiration in dopaminergic cultures.

Together, these results reinforce the growing therapeutic value of combining precision AI technologies with diversified non-dopaminergic strategies to address the complex biological landscape of Parkinson's disease.

Strategy	Implementation	Impact
AI-Designed Drug Discovery	Deep learning screening of molecular libraries; reinforcement-learning optimization; target prediction for α-synuclein, LRRK2, GCase	Accelerates identification of disease-modifying candidates; reduces off-target toxicity; enables rapid preclinical advancement
AI-Optimized Neuromodulation	Algorithm-guided DBS parameter programming; adaptive stimulation based on real-time neural signals	25–30% tremor reduction; improved gait stability; decreased stimulation-related side effects
Glutamatergic Modulation	NMDA receptor antagonists; amantadine ER formulations	Reduces dyskinesias; improves motor fluctuations; decreases excitotoxicity
Adenosine A2A Antagonism	Selective A2A-receptor inhibitors adjunct to levodopa	Shortens "off" time; enhances motor performance without worsening dyskinesia
Serotonergic and Cholinergic Modulation	5-HT receptor ligands; cholinesterase stabilization; nicotinic receptor agents	Improves tremor, gait freezing, executive dysfunction; beneficial for cognitive and autonomic symptoms
Anti-Inflammatory & Microglial	TNF-α inhibitors; microglial-stabilizing small molecules	Reduces neuroinflammation; slows α-synuclein propagation; improves

Strategy	Implementation	Impact
Modulation		neuroprotective environment
Computationally Modeled Combination Therapy	AI-driven modeling of synergistic drug pairs; selection of minimal-dose multidomain regimens	Enhances treatment response; lowers dopaminergic load; reduces risk of long-term motor complications

Discussion. The findings highlight AI-driven drug discovery and non-dopaminergic interventions as pivotal developments for advancing Parkinson's disease treatment. AI systems overcome major limitations of conventional therapeutics by enabling rapid molecular screening, predicting clinical outcomes, and individualizing treatment selection. These technologies accelerate the identification of compounds that modulate central disease mechanisms such as α-synuclein aggregation, mitochondrial failure, lysosomal dysfunction, and neuroinflammation.

Non-dopaminergic approaches broaden therapeutic horizons, addressing symptoms insufficiently managed by dopaminergic therapies. Glutamate modulation reduces excitotoxicity and dyskinesias, while adenosine A2A antagonism improves motor fluctuations. Serotonergic and cholinergic modulation address tremor, gait, cognitive decline, and autonomic dysfunction—domains that significantly impair quality of life. Calcium channel blockers, synuclein immunotherapies, and mitochondrial stabilizers represent additional targets under investigation.

Emerging evidence supports integrated strategies combining AI-designed therapeutics with non-dopaminergic pharmacology and advanced neuromodulation. AI-guided selection of patient-specific treatment combinations may offer synergistic effects, reducing reliance on levodopa and delaying long-term complications. However, challenges remain, including validation of AI models across diverse populations, ethical considerations related to algorithmic decision-making, and the need for standardized regulatory frameworks.

Further research should emphasize longitudinal trials of AI-designed compounds, mechanistic characterization of non-dopaminergic targets, and harmonization of multimodal biomarkers to guide personalized interventions.

These findings collectively highlight the necessity of shifting Parkinson's disease management beyond isolated dopaminergic modulation toward integrated, mechanism-targeted strategies. AI-designed therapeutics provide unprecedented precision in identifying compounds that modulate protein misfolding, neuroinflammation, mitochondrial failure, and synaptic instability—key drivers of disease progression. Meanwhile, non-dopaminergic therapies address symptom domains often resistant to levodopa, including gait freezing, tremor variability, and cognitive decline. The convergence of computational discovery, biomarker-driven stratification, and pharmacological diversification supports a more personalized therapeutic landscape. Continued validation in large, multi-center trials will be essential to determine long-term clinical impact and optimize patient-tailored treatment algorithms.

Conclusion. AI-designed therapeutics and non-dopaminergic approaches represent transformative pathways in Parkinson's disease research and clinical care. Together, they enable earlier disease interception, improved symptom management, and the potential to modify progression. Integrating data-driven drug discovery, personalized treatment modeling, and targeted neurotransmitter modulation may redefine future therapeutic standards. Continued investment in interdisciplinary research, clinical validation, and equitable implementation will be essential for realizing the full potential of these innovations.

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