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Systematic Review Article

ASSOCIATION BETWEEN PATHOPHYSIOLOGICAL MECHANISMS AND THERAPEUTIC TARGETS IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Parkinson's disease is a progressive neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability, along with non-motor manifestations including cognitive impairment and autonomic dysfunction. The underlying pathophysiology involves complex mechanisms including dopaminergic neuronal degeneration in the substantia nigra, α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, impaired protein degradation pathways, and genetic mutations. A comprehensive synthesis linking specific pathophysiological mechanisms to therapeutic targets is essential to guide future translational research and precision-based interventions. **Objectives:** This systematic review aims to evaluate and synthesize the existing evidence on the association between key pathophysiological mechanisms in Parkinson's disease and their corresponding therapeutic targets. It also seeks to identify emerging molecular and cellular targets, determine the stage of therapeutic development and highlight current gaps in translating mechanistic insights into effective clinical therapies.

Material and Methods: This systematic review was conducted according to PRISMA guidelines. Electronic databases (PubMed, Scopus, Web of Science, and Embase) were searched for experimental, translational, and clinical studies on mechanistic pathways and related therapies in Parkinson's disease. Studies were screened using predefined criteria, data were extracted on mechanisms, targets, interventions, and outcomes, and quality was assessed with appropriate risk-of-bias tools. Findings were synthesized narratively.

Results: Parkinson's disease is characterized by α-synuclein aggregation, dopaminergic neuron loss, mitochondrial dysfunction (Complex I deficiency), oxidative stress, neuroinflammation, autophagic impairment, and genetic susceptibility. Gut–brain axis involvement and low cerebrospinal fluid amyloid-β42 levels are associated with cognitive decline.

Levodopa remains the most effective symptomatic therapy but is limited by motor fluctuations and wearing-off. Continuous dopaminergic strategies, adjunct medications, Levodopa–Carbidopa Intestinal Gel (LCIG) infusion, and deep brain stimulation provide significant improvement in motor and non-motor symptoms and quality of life in advanced disease. Emerging disease-modifying approaches—including antioxidant, anti-inflammatory, and gene-based therapies have shown promising early results, supporting further development.

Conclusions: Levodopa and dopamine agonists remain central for motor control in Parkinson's disease, with other agents managing fluctuations and neuropsychiatric symptoms, though evidence is limited. Advances targeting non-dopaminergic and kinase pathways are ongoing, but true neuroprotection remains elusive. Non-motor symptoms significantly affect quality of life, underscoring the need for effective disease-modifying therapies.

Keywords: Parkinson's disease, pathophysiological mechanisms, therapeutic targets, dopaminergic neurodegeneration, α-synuclein aggregation, neuroinflammation, gene therapy.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized clinically by bradykinesia, resting tremor, rigidity, and postural instability.

Parkinson disease is the second most common neurodegenerative disorder, affecting 2–3% of individuals over 65 years. It is marked by loss of dopaminergic neurons in the substantia nigra and accumulation of α-synuclein aggregates, leading to dopamine deficiency. Diagnosis is based on bradykinesia and other motor features, though non-motor symptoms significantly increase disability. Its pathogenesis involves multiple mechanisms, including mitochondrial dysfunction, oxidative stress, impaired α-synuclein processing, and neuroinflammation (Poewe W et al., 2017).[1]

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease, with a multifactorial etiology involving genetic, environmental, and immunologic factors. Emerging evidence highlights a role for immune-mediated mechanisms in neuronal degeneration. It is characterized by loss of dopaminergic neurons in the substantia nigra and accumulation of α-synuclein–containing Lewy bodies. Clinically, patients develop bradykinesia, rigidity, and resting tremor, along with nonmotor symptoms such as cognitive, psychiatric, olfactory, and autonomic dysfunction. The disease progresses over time, and current treatments provide symptomatic relief without modifying disease progression (De Virgilio A et al., 2016).[2]

Parkinson disease is a clinically heterogeneous disorder with variable rates of progression. Management includes pharmacologic therapy—primarily levodopa, alone or combined with other agents—and supportive nonpharmacologic interventions such as exercise and rehabilitation therapies. For patients with refractory tremor, motor fluctuations, or dyskinesias, advanced treatments like deep brain stimulation and levodopa–carbidopa intestinal infusion may provide benefit (Armstrong MJ et al., 2020).[3]

Parkinson disease is a progressive neurodegenerative condition associated with substantial morbidity and mortality. Diagnosis is primarily clinical and based on cardinal motor features such as bradykinesia, rigidity, and tremor. Although motor symptoms define the disorder, nonmotor manifestations—including autonomic disturbances, depression, and hallucinations—are common and may complicate early recognition. Disease progression varies widely, and clinical features alone do not reliably predict its course (Halli-Tierney AD et al., 2020).[4]

Deep brain stimulation is useful for patients with inadequately controlled symptoms despite medical therapy. Rehabilitation therapies support functional independence. Common nonmotor symptoms—such as fatigue, sleep disturbances, cognitive impairment, and depression—reduce quality of life but may improve with treatment (Gazewood JD et al., 2013).[5]

Understanding the relationship between specific pathophysiological pathways and emerging therapeutic targets is critical for advancing precision medicine in PD. A systematic synthesis of current evidence linking molecular mechanisms to therapeutic interventions may clarify translational gaps and identify promising strategies for disease modification.

Therefore, this systematic review aims to evaluate the association between key pathophysiological mechanisms and corresponding therapeutic targets in Parkinson's disease, providing an integrated overview of current evidence and future directions.

Objectives

This systematic review evaluates and integrates existing evidence on the link between major pathophysiological mechanisms in Parkinson's disease and their related therapeutic targets. It further identifies emerging molecular and cellular targets, examines the stage of their therapeutic development, and highlights gaps in translating mechanistic discoveries into effective clinical interventions.

MATERIALS AND METHODS

This systematic review conducted in accordance with PRISMA guidelines. A comprehensive literature search was performed in electronic databases including PubMed, Scopus, Web of Science, and Embase using key words Parkinson's disease, pathophysiological mechanisms, therapeutic targets, dopaminergic neurodegeneration, α-synuclein aggregation, neuroinflammation, gene therapy. Eligible study designs included randomized controlled trials, cohort studies, case–control studies, experimental studies and cross-sectional studies, review articles. Non-English papers without extractable data, lacked clear outcome measures or evaluable results, editorials, commentaries, conference abstracts, were excluded.

Titles, abstracts, and full texts were independently screened by two reviewers, with disagreements resolved by consensus. Data extraction and quality assessment were performed independently using standardized tools appropriate to study design. Due to heterogeneity among studies, a qualitative synthesis was conducted.

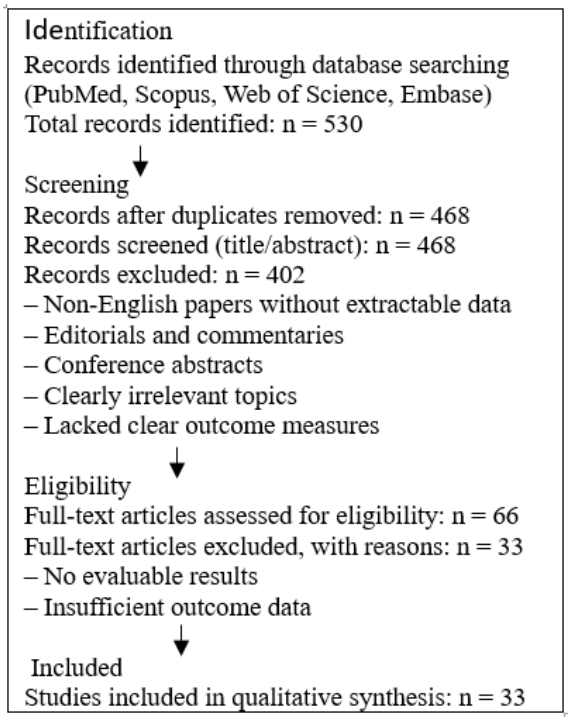

Figure 1: PRISMA flow diagram of study selection process

RESULTS AND DISCUSSION

Pathophysiological mechanisms

PD is characterized by α-synuclein–containing Lewy bodies in the midbrain and progressive dopaminergic neuron loss. Evidence indicates a role for adaptive immunity, as CD4+ T-cell infiltration and responses to modified α-synuclein contribute to neurodegeneration. Early nonmotor features, particularly gastrointestinal dysfunction, are common and linked to enteric neuronal loss, Lewy body deposition in the gut, and alterations in gut microbiota, supporting a gut–brain connection in disease pathogenesis (Campos-Acuña J et al., 2019).[6]

Parkinson's disease is caused by degeneration of dopaminergic neurons in the substantia nigra. Current therapies are symptomatic and do not prevent neuronal loss, partly due to limited understanding of key molecular mechanisms. Evidence implicates protein misfolding, ubiquitin–proteasome dysfunction, mitochondrial impairment, and oxidative stress in pathogenesis. Neurotoxin and gene-based models have helped clarify pathways of dopaminergic neurodegeneration and selective neuronal vulnerability (Dauer W et al., 2003).[7]

Postmortem analysis of the substantia nigra in patients with Parkinson's disease showed a selective reduction in mitochondrial Complex I activity, while overall protein content, mitochondrial mass, and other respiratory-chain activities remained largely unchanged. This specific impairment mirrors the defect observed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism models, supporting the hypothesis that environmental toxins with similar mechanisms may contribute to Parkinson's disease pathogenesis (Schapira AH et al., 1990).[8]

Immunohistochemical analysis of α-synucleinopathies—including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy—demonstrated variable clusterin (apolipoprotein J) expression within pathological inclusions. Approximately half of cortical Lewy bodies in dementia with Lewy bodies showed clusterin positivity, whereas brainstem Lewy bodies in Parkinson's disease and dementia with Lewy bodies rarely did. In multiple system atrophy, clusterin was detected in a subset of glial cytoplasmic inclusions. Its distribution often overlapped with α-synuclein, particularly in cortical Lewy bodies, suggesting that clusterin may influence α-synuclein aggregation, potentially through its proposed chaperone function (Sasaki K et al., 2002).[9]

Oxidative stress is a key contributor to dopaminergic neuron degeneration in Parkinson's disease. Impaired redox balance leads to oxidative and nitrative damage within the substantia nigra, disrupting vital cellular processes and promoting cell death. Reactive oxygen species arise from multiple sources, including dopamine metabolism, mitochondrial dysfunction, iron accumulation, neuroinflammation, calcium imbalance, and aging. Mutations in PD-related genes such as DJ-1, PTEN-induced putative kinase 1 (PINK1), parkin, α-synuclein, and Leucine-rich repeat kinase 2 (LRRK2) further impair mitochondrial function and increase vulnerability to oxidative stress. In turn, oxidative damage disrupts cellular quality-control systems, including the ubiquitin–proteasome pathway and mitophagy (Dias V et al., 2013).[10]

Neuroinflammation contributes to dopaminergic neuron loss in Parkinson's disease through activation of glial and immune cells. This response promotes oxidative stress and cytokine-mediated apoptosis, driving disease progression. Immunomodulatory strategies may help slow this process (Hirsch EC et al., 2009).[11]

Autophagy, particularly macroautophagy, involves the sequestration of cytoplasmic proteins and organelles into double-membraned autophagosomes that fuse with lysosomes for degradation. These vesicles arise from membranes derived from sources such as the endoplasmic reticulum, mitochondria, plasma membrane, and Golgi apparatus. Autophagic dysfunction has now been reported in a number of neurodegenerative diseases (Frake RA et al., 2015).[12]

Over the past decade and a half, major advances have clarified the genetic contributors to Parkinson's disease. Although mutations in genes such as SNCA, PINK1, PARK2, PARK7, PLA2G6, FBXO7, and ATP13A2 account for relatively uncommon forms of the disorder, variants in LRRK2—particularly in specific ethnic groups—represent one of the more frequent genetic causes (Singleton AB et al., 2013).[13]

Low cerebrospinal fluid amyloid-β42 levels, indicating coexisting Alzheimer pathology, are linked to future cognitive decline and dementia in Parkinson's disease. Genetic factors such as apolipoprotein E (APOE ε4), glucosylceramidase (GBA) mutations, and α-synuclein (SNCA) variants are also associated with increased risk, while evidence for microtubule-associated protein tau (MAPT) is inconsistent (Aarsland D et al., 2017).[14]

Therapeutic Targets

Levodopa remains the most effective treatment for motor symptoms of Parkinson's disease; however, in selected patients—such as those with mild disease, predominant tremor, or younger age—alternative agents (e.g., Monoamine Oxidase-B [MAO-B] inhibitors, dopamine agonists, amantadine, anticholinergics, or β-blockers) may be used initially to delay motor complications. Motor fluctuations can be addressed by adjusting levodopa dosing or adding adjunct therapies such as MAO-B inhibitors, Catechol-O-Methyltransferase (COMT) inhibitors, or dopamine agonists. Impulse control disorders are usually managed by reducing or discontinuing dopaminergic medications. Management of nonmotor symptoms is often limited by insufficient high-quality evidence (Connolly BS et al., 2014).[15]

Many neuroprotective agents for Parkinson's disease have shown preclinical promise but failed in clinical trials, likely due to incomplete understanding of disease mechanisms, reliance on toxin-based models, and lack of validated progression biomarkers. Although therapies for Parkinson's disease dementia have had limited success, emerging links between tau, amyloid-β, and cognitive decline may provide new treatment targets (Athauda D et al., 2015).[16]

Recognition of striatal dopamine deficiency in Parkinson's disease led to dopamine replacement strategies such as levodopa, dopamine agonists, and MAO-B inhibitors. New formulations and delivery methods aim to reduce long-term complications of these therapies. Overactivity of glutamatergic pathways has also been implicated, supporting the use of glutamate antagonists. Growing evidence links oxidative stress to disease progression, and future research is focused on neuroprotective approaches, including MAO-B inhibitors, iron chelators, and antioxidant therapies, to slow neurodegeneration (Riederer P et al., 1993).[17]

Management of early Parkinson's disease should consider the potential neuroprotective effects of MAO-B inhibitors, the oxidative metabolism of dopamine, and the risk of long-term levodopa-related complications. Early use of agents that provide sustained dopaminergic stimulation may help delay adverse effects. Treatment strategies aim to balance possible neuroprotection with effective symptomatic control (Olanow CW, 1992).[18]

Wei YJ et al., 2010, concluded that nearly half of elderly Medicare beneficiaries with Parkinson's disease in this study did not receive antiparkinsonian medications between 2000 and 2003. Levodopa was the most commonly prescribed agent, used alone or with other therapies. Factors influencing medication use included age, education level, prescription coverage, functional status, cognitive impairment, depression, and institutional residence, highlighting targets for improving care delivery.[19]

The theory of continuous dopaminergic stimulation suggests that steady, non-pulsatile delivery of dopaminergic therapy may reduce the development of motor complications. Evidence from MPTP-treated primate models and clinical studies in Parkinson's disease shows that long-acting or continuously infused dopaminergic agents are associated with fewer motor fluctuations. The key challenge remains the development of an oral levodopa formulation that ensures sustained drug delivery while minimizing motor complications (Olanow CW et al., 2006).[20]

Dopamine agonists have longer plasma half-lives than levodopa, providing more sustained receptor stimulation and potentially reducing motor complications. Clinical evidence also suggests possible neuroprotective effects. While treatment choice should be individualized, dopamine agonists are often recommended as initial therapy in Parkinson's disease (Kondo T, 2002).[21]

Levodopa is effective in Parkinson's disease, but over time many patients develop "wearing-off," where each dose provides shorter relief. Though once considered a late-stage feature, it can also occur in early, seemingly well-controlled disease (Stocchi F et al., 2010).[22]

Combination therapy with a dopamine agonist and levodopa/Dopa-Decarboxylase Inhibitor (DCI) is widely used, but DCI may contribute to motor fluctuations due to greater variability in plasma levodopa levels. In a small series of six patients with significant motor complications on levodopa/DCI, switching directly to levodopa without DCI (starting at a 1:4 ratio and titrating upward) improved wearing-off symptoms in most cases, except for two who discontinued early (Hironishi M et al., 2002).[23]

In a multinational registry of 375 advanced Parkinson's disease patients (258 completed 24 months), Levodopa–carbidopa intestinal gel (LCIG) significantly reduced daily "Off" time (−4.1 h), "On" time with dyskinesia (−1.1 h), non-motor symptom burden, and Parkinson's Disease Questionnaire-8 (PDQ-8) quality-of-life scores (all $P \leq 0.006$). Treatment-related adverse events occurred in 54% of patients, most commonly weight loss (6.7%), device infections (5.9%), device dislocation (4.8%) and device issues (4.8%), and polyneuropathy (4.5%). LCIG provided sustained improvement in motor fluctuations, non-motor symptoms (notably sleep, mood, cognition, and gastrointestinal issues), and quality of life over 24 months in advanced Parkinson's disease, with a safety profile consistent with previous reports (Antonini A et al., 2017).[24]

The observational study by Antonini A et al., 2016, supports the long-term safety and effectiveness of LCIG infusion in advanced Parkinson's disease,

demonstrating sustained improvements in motor symptoms, non-motor features, and quality of life.[25] Deep brain stimulation (DBS) is the most effective surgical therapy for advanced Parkinson's disease. The primary targets are the subthalamic nucleus and globus pallidus internus, while thalamic stimulation (ventral intermediate nucleus) is mainly used for tremor-dominant elderly patients. Long-term studies demonstrate sustained improvement in motor symptoms, fluctuations, and dyskinesia with subthalamic stimulation, though potential psychiatric effects highlight the need for a skilled multidisciplinary team. Emerging evidence that pedunculopontine nucleus stimulation may improve axial symptoms, even in levodopa-resistant cases, offers additional promise for advanced disease management (Moro E et al., 2006).[26]

Subthalamic nucleus deep brain stimulation is an established therapy for motor fluctuations, dyskinesia, and refractory tremor in Parkinson's disease. Best outcomes are seen in younger patients with good levodopa responsiveness and preserved cognition, and in such cases, it outperforms standard medical therapy in maintaining quality of life (Volkmann J, 2007).[27]

Disease-modifying strategies in Parkinson's disease include targeting glial cell–derived neurotrophic factor (GDNF), as direct delivery has shown symptomatic benefit. Regulated expression systems, such as tetracycline-controlled transactivators, have been explored to optimize GDNF infusion. Gene therapy offers a promising alternative to conventional treatments like levodopa, MAO-B inhibitors, and anticholinergics, potentially reducing treatment-related adverse effects. This approach focuses on the genetic mechanisms of Parkinson's disease and emerging gene-based therapeutic models (Dumbhare O et al., 2023).[28]

Four gene therapy approaches are under clinical evaluation in Parkinson's disease, including viral delivery of Aromatic L-Amino Acid Decarboxylase (AADC), Glutamic Acid Decarboxylase (GAD), neurturin, and a lentiviral construct encoding key dopamine-synthesizing enzymes. GAD showed motor improvement in phase II trials, while neurturin demonstrated delayed benefits; other strategies reported positive early-phase results with no major surgical safety concerns. These findings support ongoing development of gene-based therapies for PD (Nakata Y et al., 2012).[29]

Table 1: Summary of Key Studies on Therapeutic Strategies and Emerging Targets in Parkinson's Disease

Author	Key Findings
Connolly BS et al., 2014	Levodopa remains the most effective treatment for motor symptoms. Dopamine agonists and metabolism inhibitors help manage motor fluctuations. Management of nonmotor symptoms is often limited by insufficient high-quality evidence.
Athauda D et al., 2015	Many neuroprotective agents showed preclinical promise but failed in clinical trials due to incomplete understanding of disease mechanisms and lack of validated progression biomarkers. Emerging links between tau, amyloid-β, and cognitive decline may provide new treatment targets.
Riederer P et al., 1993	Dopamine replacement strategies were developed based on striatal dopamine deficiency. Overactivity of glutamatergic pathways, supporting the use of glutamate antagonists. Oxidative stress are implicated in disease progression, supporting neuroprotective approaches.
Olanow CW, 1992	Early management should consider potential neuroprotective effects of MAO-B inhibitors and risks of long-term levodopa complications. Sustained dopaminergic stimulation may help delay adverse effects.
Wei YJ et al., 2010	Nearly half of elderly Medicare beneficiaries with PD did not receive antiparkinsonian medications. Levodopa was most commonly prescribed, and medication use was influenced by demographic and clinical factors.
Olanow CW et al., 2006	Continuous dopaminergic stimulation may reduce motor complications. Long-acting or continuous infusion therapies are associated with fewer motor fluctuations.
Kondo T, 2002	Dopamine agonists have longer plasma half-lives than levodopa and may reduce motor complications. They are often recommended as initial therapy depending on patient condition.
Stocchi F et al., 2010	Wearing-off occurs when each levodopa dose provides shorter relief. It may appear even in early, seemingly well-controlled disease.
Hironishi M et al., 2002	Switching from levodopa/DCI to levodopa without DCI improved wearing-off symptoms in most patients with motor complications.
Antonini A et al., 2017	LCIG significantly reduced "Off" time, dyskinesia, non-motor symptoms, and improved quality of life over 24 months. Safety profile was consistent with previous reports.
Antonini A et al., 2016	Observational data supported long-term safety and effectiveness of LCIG infusion with sustained motor and non-motor improvements.
Moro E et al., 2006	Deep brain stimulation improves motor symptoms and fluctuations in advanced PD. Emerging pedunculopontine nucleus stimulation may benefit axial symptoms.
Volkmann J, 2007	Subthalamic nucleus DBS is superior to standard medical therapy in selected patients, improving quality of life.
Dumbhare O et al., 2023	GDNF-based gene therapy represents a promising disease-modifying strategy with potential reduction in adverse effects compared to conventional therapies.
Nakata Y et al., 2012	Gene therapy approaches (AADC, GAD, neurturin, lentiviral systems) showed motor improvement in early trials with no major surgical safety concerns.

The prevalence of asymptomatic bacteriuria was 10.5% in antenatal women compared to only 2.3% in non-pregnant women in the age group of 20-25 years. It was 22.1% vs. 3.6% in 26-35 years of age group. It was 17.6% vs. 3.2% in low-income group and null in higher income group in both groups. It was more in third trimester compared to first and second trimester. It was more in primi compared to multi.

CONCLUSION

Strong evidence supports the use of levodopa and dopamine agonists for motor symptoms across all

stages of Parkinson's disease. Dopamine agonists and dopamine-metabolism inhibitors help manage motor fluctuations, while clozapine is effective for hallucinations. Cholinesterase inhibitors may benefit dementia, and antidepressants or pramipexole can improve depressive symptoms. Evidence for other motor and nonmotor treatments remains limited (Connolly BS et al., 2014).[15]

Better treatment of levodopa-resistant symptoms in Parkinson's disease depends on improved understanding of underlying mechanisms. Future therapies may target non-dopaminergic systems such as serotonin and adenosine pathways. Limited progress in neuroprotection reflects inadequate disease models and lack of reliable biomarkers, and most emerging gene therapies remain largely symptomatic rather than disease-modifying (Stoessl J, 2008).[30]

Advances in Parkinson's disease research highlight the role of disrupted kinase activity and phosphorylation pathways in its pathogenesis. Several PD-associated genes, including PINK1, LRRK2, GAK, SNCA, and DJ-1, influence signaling networks such as MAPK and AKT pathways. Downstream MAPK components—particularly JNK and p38—are closely linked to neuronal death, making them potential therapeutic targets. Extracellular Signal–Regulated Kinase (ERK) signaling is implicated in levodopa-induce dyskinesia, and its inhibition has shown benefit in experimental models (Wang G et al., 2012).[31]

Non-motor symptoms in Parkinson's disease are often overlooked and inadequately managed. While some—such as depression, constipation, pain, urinary, and sleep problems—respond to current therapies, others require new non-dopaminergic strategies. Long-term control will likely depend on effective disease-modifying treatments (Chaudhuri KR et al., 2006).[32]

Non-motor symptoms significantly impact quality of life and disability in Parkinson's disease, affecting both patients and caregivers. Effective management requires their prompt recognition and appropriate treatment (Salawu FK et al., 2010).[33]

In conclusion, Levodopa and dopamine agonists remain the mainstay for motor symptoms in Parkinson's disease, with additional agents addressing fluctuations, psychosis, dementia, and depression, though evidence for many therapies is limited. Future strategies aim to target non-dopaminergic pathways and kinase signaling, but progress in neuroprotection has been constrained by inadequate models and biomarkers, and most gene therapies remain symptomatic. Non-motor symptoms substantially impair quality of life, highlighting the need for better recognition and disease-modifying treatments.

Future research should prioritize identifying reliable disease-modifying targets and biomarkers for progression and treatment response. Well-designed clinical trials are needed to evaluate emerging gene-based and neuroprotective therapies, with particular focus on levodopa-resistant and non-motor symptoms to improve long-term outcomes.

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