J. Pharm. Res. 2026;25(4):219-228

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

SYSTEMATIC REVIEW

Differential Epidemiology, Pathophysiology, Clinical Characteristics, and Therapeutic Outcomes in Early-Onset and Late-Onset Parkinson's Disease: A Systematic Comparative Review

Renu Kumari[1], Nirmal Dongre[2], Souravh Bais[3*]

[1]*Research Scholar, Department of Pharmacology, Institute of Pharmaceutical Sciences, SAGE University, Indore, Madhya Pradesh, India*

[2]*Professor, Department of Pharmacognosy, Institute of Pharmacy, SAGE University, Indore, Madhya Pradesh, India*

[3]*Professor, Department of Pharmacology, Institute of Pharmaceutical Sciences, SAGE University, Indore, Madhya Pradesh, India*

ARTICLE INFO

Article history:
Received 31-07-2026
Accepted 20-08-2026
Published 28-10-2026

** Corresponding author.*
Souravh Bais
souravhbais@gmail.com

https://doi.org/10.18579/jopcr/v25.i4.165

© 2026 Published by Krupanidhi College of Pharmacy. This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/)

ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder with marked clinical heterogeneity influenced by age at disease onset. Early-Onset Parkinson's Disease (EOPD), typically diagnosed before 50 years of age, differs substantially from Late-Onset Parkinson's Disease (LOPD) in its genetic basis, clinical manifestations, disease progression, therapeutic response, and socioeconomic consequences. A systematic comparative review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Published comparative cohort studies, epidemiological investigations, systematic reviews, and related clinical studies evaluating EOPD and LOPD were identified through searches of PubMed/MEDLINE, Web of Science, and Google Scholar. Eligible studies were selected using predefined PICOS criteria, and the available evidence was synthesized primarily through narrative analysis because of methodological and clinical heterogeneity across studies. The reviewed evidence demonstrates that EOPD is strongly associated with monogenic mutations, particularly PRKN, PINK1, DJ-1, and LRRK2, whereas LOPD is predominantly influenced by aging-related neurodegenerative mechanisms and cumulative environmental exposures. Individuals with EOPD generally exhibit slower disease progression, better preservation of cognitive function, and greater responsiveness to dopaminergic therapy but experience a higher incidence of levodopa-induced dyskinesia and motor fluctuations during long-term treatment. In contrast, LOPD is characterized by accelerated clinical progression, greater cognitive decline, psychosis, autonomic dysfunction, gait impairment, and increased healthcare utilization. Deep Brain Stimulation demonstrates greater suitability and long-term benefit in carefully selected patients with EOPD, while socioeconomic burden differs substantially between the two groups, with indirect productivity loss predominating in EOPD and direct medical costs being more prominent in LOPD. EOPD and LOPD represent biologically and clinically distinct phenotypes of Parkinson's disease that require individualized diagnostic approaches, age-specific therapeutic strategies, and targeted long-term management. Future research should emphasize standardized age-at-onset definitions, longitudinal cohort studies, and the development of precision medicine approaches to improve outcomes across both patient populations.

Keywords: Early-Onset Parkinson's Disease; Late-Onset Parkinson's Disease; Parkinson's Disease; Age at Onset; Levodopa-Induced Dyskinesia; Deep Brain Stimulation

INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease and represents a major global public health challenge due to its increasing incidence and associated disability. The disease is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in dopamine depletion within the nigrostriatal pathway and the accumulation of intracellular α-synuclein aggregates known as Lewy bodies. These neuropathological changes give rise to a combination of motor manifestations, including bradykinesia, resting tremor, muscular rigidity, and postural instability, together with a broad spectrum of non-motor symptoms such as cognitive impairment, depression, sleep disturbances, autonomic dysfunction, anosmia, and psychiatric complications. The growing burden of PD has become a major concern because of increased life expectancy and the ageing global population, making it one of the fastest-growing neurological disorders worldwide[1-3].

Although Parkinson's disease has traditionally been regarded as a disorder of older adults, substantial clinical heterogeneity exists based on the age at disease onset. Approximately 5–10% of patients develop symptoms before the age of 50 years and are classified as having Early-Onset Parkinson's Disease (EOPD), whereas the majority of cases present after 60 years of age and are categorized as Late-Onset Parkinson's Disease (LOPD). Increasing evidence indicates that these two clinical phenotypes differ considerably with respect to epidemiology, genetic susceptibility, molecular pathogenesis, clinical presentation, therapeutic response, and long-term prognosis. Consequently, age at onset has emerged as an important determinant of disease phenotype and clinical management [4-7].

The biological mechanisms underlying EOPD and LOPD are also distinct. Early-onset disease is frequently associated with inherited mutations in genes involved in mitochondrial function and protein homeostasis, including PRKN (Parkin), PINK1, DJ-1 (PARK7), and LRRK2. These genetic abnormalities contribute to impaired mitochondrial quality control, oxidative stress, defective autophagy, and neuronal vulnerability at a younger age. In contrast, LOPD is predominantly influenced by age-related neurodegenerative processes, including mitochondrial dysfunction, chronic neuroinflammation, impaired proteostasis, oxidative damage, and cumulative environmental exposures. These mechanisms collectively accelerate neuronal degeneration and contribute to the more aggressive disease course observed in older individuals [8-12].

Clinically, patients with EOPD often exhibit slower disease progression, better preservation of cognitive function, and a more favourable response to dopaminergic therapy during the early stages of disease. However, because of prolonged exposure to levodopa, they are more susceptible to developing levodopa-induced dyskinesia and motor fluctuations over time. Conversely, patients with LOPD generally experience more rapid motor deterioration, postural instability, gait impairment, cognitive decline, autonomic dysfunction, hallucinations, and increased functional disability. These age-related differences have important implications for individualized therapeutic decision-making, long-term follow-up, and healthcare planning [13-17].

The socioeconomic impact of Parkinson's disease also varies according to the age of onset. Individuals diagnosed with EOPD frequently develop symptoms during their economically productive years, resulting in substantial indirect costs associated with loss of employment, reduced productivity, caregiver burden, and impaired quality of life. In contrast, LOPD is associated with higher direct healthcare expenditures due to hospitalization, management of multiple comorbidities, institutional care, and increasing dependency during advanced stages of the disease. Recognition of these contrasting economic and psychosocial consequences is essential for developing effective healthcare policies and patient-centred management strategies [18–20].

Despite the increasing recognition of age-related heterogeneity in Parkinson's disease, many published studies continue to evaluate PD as a single clinical entity, thereby limiting the understanding of important biological and therapeutic differences between EOPD and LOPD. Furthermore, inconsistencies in diagnostic criteria, age-at-onset definitions, and outcome measures have hindered direct comparison among available studies. A systematic synthesis of the current evidence is therefore necessary to clarify the differential epidemiology, pathophysiological mechanisms, clinical manifestations, treatment outcomes, and socioeconomic burden associated with these two phenotypes [21-23].

Therefore, the present systematic comparative review aims to critically evaluate and integrate the available evidence regarding the epidemiology, genetic architecture, molecular pathophysiology, clinical characteristics, therapeutic strategies, and long-term outcomes of Early-Onset and Late-Onset Parkinson's Disease. By identifying similarities, differences, and current knowledge gaps, this review seeks to provide a comprehensive scientific framework that supports precision medicine approaches, facilitates individualized patient care, and highlights priorities for future clinical and translational research [24-26].

MATERIALS AND METHODS (JPR-REVISED VERSION)

Methodology: Adherence to PRISMA Guidelines

Protocol and Reporting Standards:

This comprehensive comparative analysis was conducted following the guiding principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, ensuring methodological transparency and rigor of the study. This study aimed to systematically collate, evaluate, and synthesize data from published studies comparing EOPD and LOPD cohorts 29.

- Records identified from databases: PubMed/MEDLINE (n = 845), Web of Science (n = 612), Google Scholar (n = 420), Total records identified: (n = 1,877)
- Records removed before screening: Duplicate records removed: (n = 715)
- Records removed for other reasons (e.g., automated tools for non-English/non-human studies): (n = 42)
- Records remaining for screening: (n = 1,120)

Screening:

- Titles and abstracts screened: (n = 1,120)

Note: Independent screening was conducted based on the PICOS framework.

- Records excluded at title/abstract stage: (n = 982)

Eligibility:

- Full-text reports sought for retrieval: (n = 138)
- Full-text reports not retrieved: (n = 12)
- Reason 1 (Not accessible/Paywall): (n = 8)
- Reason 2 (Letter to editor/Conference abstract only): (n = 4)
- Full-text reports assessed for eligibility: (n = 126)

Note: Assessed against full inclusion/exclusion criteria.

Full-text reports excluded (with reasons): (n = 88)

- Reason 1 (Did not use standardized AAO cutoffs): (n = 34)
- Reason 2 (Combined EOPD/LOPD data without separation): (n = 26)
- Reason 3 (Incorrect study design, e.g., single-case reports): (n = 18)
- Other specific reasons (Insufficient outcome data): (n = 10)

Inclusion:

- Total studies included in the review: (n = 38)
- Studies included in quantitative synthesis (prevalence/complication rates): (n = 14)
- Studies included in narrative review only (due to heterogeneity): (n = 24)

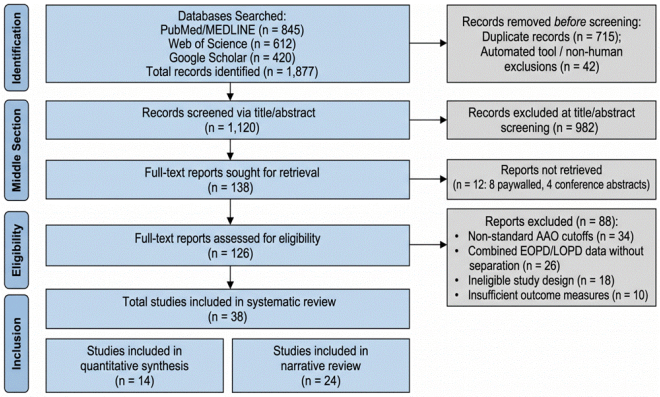


Fig. 1 PRISMA 2020 flow diagram illustrating the identification, screening, eligibility, and inclusion process for comparative studies evaluating Early-Onset Parkinson's Disease (EOPD) and Late-Onset Parkinson's Disease (LOPD)

Eligibility Criteria (PICOS Framework)

The literature search and inclusion criteria were defined *a priori* based on the following Population, Intervention/Exposure, Comparator, Outcome, and Study Design (PICOS) framework:

Population (P): Studies enrolling patients diagnosed with Parkinson's disease (PD).

Exposure/Comparator (I/C): Studies explicitly comparing cohorts based on Age at Onset (AAO). The defined threshold for early onset Parkinson'sdisease (EOPD) was AAO after 21 years but before 50 years , and the Late-Onset Parkinson's disease (LOPD) comparator cohort included patients with an AAO of 50 years or older.

Outcomes (O): Key outcomes of interest included but were not limited to:

Epidemiological Trends: Incidence, prevalence, mortality, and Disability-Adjusted Life Years (DALYs) stratified by age and sex.

Etiology and Genetics: Prevalence of monogenic determinants (e.g., PRKN, *PINK1, LRRK2)* and non-genetic risk factors (e.g., head injury, smoking).

Clinical Phenotype: Comparison of initial motor symptoms (tremor vs. rigidity), non-motor symptom profiles (ICDs, psychosis, cognitive status), and disease progression velocity.

Therapeutic Response: Rates of Levodopa-Induced Dyskinesia (LID) and motor fluctuations and candidacy/outcomes for Deep Brain Stimulation (DBS).

Socioeconomic Impact: Quality of Life (QoL) metrics (PDQ-39) and occupational/economic burden.

Study Design (S): This included comparative cohort studies, large-scale epidemiological analyses, systematic reviews, and meta-analyses. Single-case reports and studies without explicit comparison groupswere excluded.

Key Alignment Details:

Standardized AAO Cutoffs (Exclusion Reason 1): Your exclusion of 34 reports at the eligibility stage based on standardized Age-at-Onset (AAO) cutoffs perfectly addresses the potential bias from inconsistent data noted in your Methodology (Section 2.4).

Data Heterogeneity (Section 2.5): The inclusion box explicitly breaks down the final 38 studies, showing how many contributed to the quantitative data in your comparative tables (n=14) versus how many were synthesized via narrative review only (n=24) due to heterogeneity. This directly supports your stated synthesis plan (Fig. 1).

Search Strategy and Data Sources

An exhaustive search was conducted across major biomedical literature databases, including PubMed/MEDLINE, Web of Science, and Google Scholar. The search strategy employed combinations of Medical Subject Headings (MeSH) terms and keywords, such as: ("Parkinson's Disease" OR "Parkinson Disease") AND ("Early-Onset" OR "Young-Onset" OR "EOPD" OR "YOPD") AND ("Late-Onset" OR "Old-Onset" OR "LOPD"). The search was not restricted to publication date to ensure a comprehensive overview of historical and recent comparative literature. Epidemiological data were obtained from robust population-based cohort reports and global burden studies.

Study Selection, Data Extraction, and Quality Assessment

Titles and abstracts were independently screened for relevance based on the PICOS criteria. Full-text articles were retrieved and assessed for final inclusion. Data extraction was performed using a standardized instrument to capture key variables (e.g., AAO cutoffs, sample size, and outcome measurements). The methodological quality was assessed based on the study design. Particular attention was paid to potential sources of bias, such as selection bias in hospital-based records versus population-based registries and interobserver variability in clinical assessments.

Data Synthesis

Owing to the heterogeneity of outcome measures, study designs, and AAO cutoffs observed across the literature, the primary approach to data synthesis was a detailed narrative review. Quantitative data, where available and consistently reported (e.g., prevalence rates, genetic frequencies, motor complication rates), were synthesized to quantify the magnitude of differences and presented in comparative tables to facilitate interpretation. The synthesis focused on identifying consistently reported phenotypic and etiological distinctions to establish the core comparative profiles of EOPD and LOPD. Only studies with acceptable methodological quality were included in the final evidence synthesis.

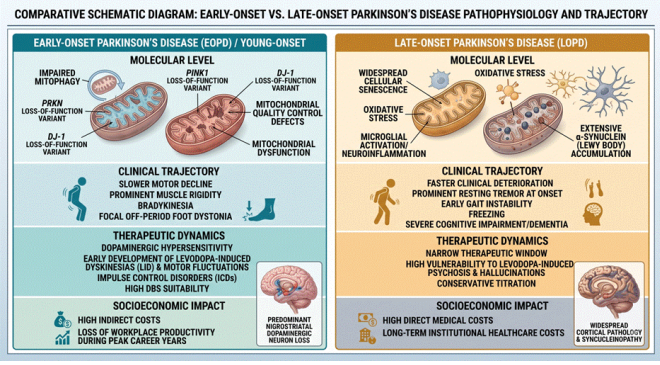


Fig. 2: Divergent clinicopathological, pharmacological, and socioeconomic trajectories of Early-Onset Parkinson's Disease (EOPD) versus Late-Onset Parkinson's Disease (LOPD). The schematic illustrates differences in underlying molecular mechanisms (mitophagy failure vs. multisystem senescent neuroinflammation), dominant motor/non-motor phenotypes, levodopa complication risk profiles, Deep Brain Stimulation eligibility, and overall economic burdens

RESULTS

Epidemiology and Demographic Characteristics

The studies included in this systematic review demonstrate that age at disease onset is a major determinant of the epidemiological and clinical heterogeneity of Parkinson's disease (PD). Early-Onset Parkinson's Disease (EOPD), generally defined as disease onset before 50 years of age, represents a relatively small proportion of PD cases, whereas Late-Onset Parkinson's Disease (LOPD) accounts for the majority of diagnoses. Despite its lower prevalence, EOPD is associated with a longer disease duration and distinctive clinical characteristics that differentiate it from LOPD.

The reviewed literature consistently indicates that genetic susceptibility contributes more significantly to EOPD, while LOPD is primarily influenced by ageing-related neurodegenerative processes and cumulative environmental factors. Consequently, patients with EOPD often present during their economically productive years, whereas LOPD predominantly affects older adults and is associated with a greater burden of age-related comorbidities.

Although EOPD patients generally experience a slower rate of disease progression, their longer survival results in prolonged exposure to dopaminergic therapy and an increased lifetime risk of treatment-related motor complications. In contrast, patients with LOPD typically exhibit faster clinical deterioration, greater functional impairment, and higher healthcare utilization because of advanced age and accompanying systemic disorders (Fig. 2).

Genetic and Molecular Differences

The reviewed evidence highlights clear molecular differences between EOPD and LOPD. EOPD demonstrates a stronger hereditary component and is frequently associated with pathogenic variants in genes involved in mitochondrial maintenance, oxidative stress regulation, and intracellular protein degradation. Among these, PRKN, PINK1, DJ-1, and LRRK2 are the most consistently implicated susceptibility genes.

In contrast, LOPD appears to result predominantly from multifactorial mechanisms involving ageing, mitochondrial dysfunction, impaired proteostasis, chronic neuroinflammation, oxidative stress, and prolonged environmental exposure. These age-related biological changes accelerate dopaminergic neuronal degeneration and contribute to the more rapid disease progression observed in older patients.

Overall, the findings indicate that although both phenotypes share common neuropathological features, their underlying molecular mechanisms differ considerably, emphasizing the need for age-specific diagnostic biomarkers and targeted therapeutic strategies.

Clinical Manifestations

Comparison of the included studies revealed marked differences in both motor and non-motor manifestations between EOPD and LOPD. Patients with EOPD generally exhibit slower progression of motor symptoms and retain functional independence for a longer period. They also demonstrate better cognitive preservation during the early stages of disease and respond more favourably to dopaminergic therapy. However, because of prolonged treatment duration, these patients experience a higher incidence of levodopa-induced dyskinesia and motor fluctuations.

Conversely, LOPD is characterized by more rapid motor deterioration, postural instability, gait impairment, cognitive decline, psychosis, autonomic dysfunction, and increased disability. Older patients frequently require earlier caregiver support and experience greater reductions in quality of life because of progressive functional dependence.

These findings demonstrate that age at onset significantly influences both the clinical phenotype and long-term disease trajectory of Parkinson's disease.

Pharmacological Management

The reviewed studies indicate that levodopa remains the cornerstone of symptomatic treatment for both EOPD and LOPD. Nevertheless, therapeutic response and long-term treatment outcomes differ according to age at onset. Patients with EOPD generally show excellent initial responsiveness to levodopa but are more likely to develop dyskinesia and motor fluctuations because of prolonged cumulative exposure. Consequently, dopamine agonists and other levodopa-sparing strategies are often considered during the early stages of treatment in younger patients.

In contrast, patients with LOPD often require individualized dose adjustment because of increased frailty, multiple comorbidities, cognitive impairment, and greater susceptibility to adverse drug reactions. Therapeutic decisions in older adults therefore focus on optimizing symptom control while minimizing treatment-related complications and maintaining functional independence.

Advanced Therapeutic Interventions

Among advanced treatment options, Deep Brain Stimulation (DBS) remains the most extensively studied surgical intervention. The reviewed evidence indicates that carefully selected patients with EOPD derive greater long-term benefit from DBS owing to their younger age, preserved cognitive function, and lower burden of systemic comorbidities. DBS effectively improves motor symptoms, reduces medication requirements, and enhances quality of life in appropriate candidates.

Although selected patients with LOPD may also benefit from DBS, treatment decisions require careful evaluation of cognitive status, medical comorbidities, and surgical risk. Overall, patient selection remains the principal determinant of favourable clinical outcomes following advanced therapeutic interventions.

Socioeconomic Burden

The included studies demonstrate that the socioeconomic consequences of Parkinson's disease differ substantially according to age at onset. EOPD predominantly affects individuals during their most productive working years, resulting in considerable indirect costs related to reduced employment, productivity loss, premature retirement, caregiver burden, and diminished quality of life.

In contrast, the economic burden associated with LOPD is driven mainly by direct healthcare expenditure, including hospitalization, long-term medical care, rehabilitation, institutional support, and management of multiple age-related comorbidities. Increased dependency and progressive disability further contribute to healthcare utilization among older patients.

Table 1: Differential Clinical and Pathophysiological Profiles

Clinical Domain	EOPD Profile Tendency	LOPD Profile Tendency	Key Mechanisms	References
Etiology	Monogenic mutations (~10%); high familial incidence	Predominantly sporadic; age-dependent risk	*PRKN/PINK1* mitophagy breakdown vs. aging-related oxidative decline	6, 8, 11
Progression Velocity	Slower clinical decline; longer duration (11.6 ± 4.69 yrs)	Rapid clinical deterioration (8.7 ± 2.8 yrs)	Slower decline supported by functional compensatory reserve	4, 10, 24
Motor Presentation	Rigidity, bradykinesia, focal off-period dystonia (33%)	Resting tremor (63%), early postural instability, gait freezing	Divergent nigrostriatal pathway vulnerability patterns	13, 14, 25
Cognitive Profiles	Preserved cognitive reserve (higher SCOPA-COG scores)	High susceptibility to cognitive decline and dementia	Accelerated cortical, limbic, and cholinergic degradation in LOPD	3, 12, 23
Behavioral & Sensory NMS	Elevated ICD risk (14.3%), depression, paresthesia (20.5%)	Levodopa-induced psychosis, hallucinations, confusion	Dopaminergic receptor hypersensitivity vs. limbic fragility	2, 11, 26

Table 2: Comparative Therapeutic Management and Socioeconomic Burden

Outcome Area	EOPD Profile	LOPD Profile	Clinical / Economic Significance	References
L-DOPA Management	Levodopa-sparing strategy; early agonist/amantadine use	Conservative titration; early levodopa initiation	Balancing motor control against dyskinesia vs. drug-induced psychosis	15, 16, 18
DBS Candidacy	High eligibility (69%); marked motor and functional benefit	Restricted eligibility (22%); frequent surgical exclusions	DBS preserves employment and reduces long-term disability in EOPD	19, 20, 21
Quality of Life (QoL)	Worse overall QoL (OR: 2.66; PDQ-39); elevated distress	Preserved relative QoL until advanced disease stages	Psychological burden of early-onset functional disability	5, 25, 26
Economic Impact	High indirect costs (lost workplace productivity)	High direct costs (hospitalization, nursing care)	Need for age-specific vocational and institutional support	1, 4, 27

Collectively, these findings highlight that EOPD and LOPD represent clinically and economically distinct phenotypes of Parkinson's disease. Recognition of these differences is essential for individualized treatment planning, healthcare resource allocation, and the development of age-specific management strategies Table. 2.

DISCUSSION

This systematic comparative review synthesizes current evidence demonstrating that EOPD and LOPD represent distinct pathophysiological and clinical phenotypes. EOPD is characterized by a strong monogenic basis, isolated nigrostriatal degeneration, high neuroplastic compensation, volatile levodopa pharmacodynamics, and substantial indirect economic burdens. LOPD is defined by multifactorial, age-related degeneration affecting widespread cortical, limbic, and cholinergic circuits, leading to early cognitive decline, dysautonomia, and high direct healthcare costs.

The present systematic comparative review highlights that Early-Onset Parkinson's Disease (EOPD) and Late-Onset Parkinson's Disease (LOPD) represent distinct clinical phenotypes with significant differences in epidemiology, genetic susceptibility, pathophysiological mechanisms, disease progression, therapeutic response, and socioeconomic burden. The findings consistently demonstrate that age at disease onset is an important determinant of disease heterogeneity and should be considered when planning diagnostic evaluation, therapeutic interventions, and long-term patient management[4-7].

One of the most consistent observations across the reviewed studies is the stronger genetic contribution to EOPD compared with LOPD. Pathogenic variants in PRKN, PINK1, DJ-1, and LRRK2 were frequently associated with younger patients, whereas late-onset disease appeared to be predominantly influenced by ageing-related biological changes, including mitochondrial dysfunction, oxidative stress, impaired protein degradation, and chronic neuroinflammation[8-11]. These findings support the concept that Parkinson's disease is not a single homogeneous disorder but comprises biologically distinct subtypes with different underlying molecular mechanisms. Consequently, genetic evaluation may be particularly valuable in younger patients presenting with a family history or atypical clinical features[9, 11].

The comparative analysis further demonstrates important differences in clinical presentation and disease progression between the two phenotypes. Patients with EOPD generally experience slower progression of motor disability, prolonged

preservation of cognitive function, and better responsiveness to dopaminergic therapy during the early stages of disease. However, prolonged exposure to levodopa substantially increases the lifetime risk of motor fluctuations and levodopa-induced dyskinesia. Conversely, patients with LOPD exhibit more rapid deterioration of motor function, earlier postural instability, greater cognitive impairment, autonomic dysfunction, and increased functional dependence, which collectively contribute to poorer clinical outcomes and reduced quality of life[12-16].

Therapeutic management should therefore be individualized according to age at disease onset. Although levodopa remains the most effective symptomatic treatment for Parkinson's disease, younger patients often benefit from levodopa-sparing strategies during the early phase of treatment to delay the development of motor complications. In contrast, treatment of LOPD requires careful dose optimization because older patients are more susceptible to adverse drug reactions, cognitive impairment, orthostatic hypotension, and drug-related hallucinations. These observations reinforce the importance of balancing symptomatic control with long-term treatment safety when selecting pharmacological interventions[15-18].

The reviewed evidence also supports the role of Deep Brain Stimulation (DBS) as an effective advanced therapeutic option, particularly in carefully selected patients with EOPD. Younger patients generally achieve greater improvement in motor symptoms, reduced medication requirements, and better long-term functional outcomes following DBS because of preserved cognitive function and fewer systemic comorbidities. Although selected patients with LOPD may also benefit from surgical intervention, comprehensive preoperative evaluation remains essential to minimize perioperative risks and optimize postoperative outcomes[19-21].

Beyond clinical outcomes, this review highlights considerable differences in the socioeconomic burden associated with age at disease onset. EOPD frequently affects individuals during their most productive years, resulting in substantial indirect costs due to reduced employment, premature retirement, caregiver burden, and loss of productivity. In contrast, LOPD is associated primarily with increased direct medical expenditure related to hospitalization, rehabilitation, long-term institutional care, and management of multiple comorbidities. Recognition of these distinct economic challenges is essential for healthcare planning and resource allocation[22–24].

The present review has several strengths. It provides a comprehensive comparison of EOPD and LOPD by integrating epidemiological, genetic, molecular, clinical, therapeutic, and socioeconomic evidence within a single systematic framework. This integrated approach facilitates a broader understanding of age-related disease heterogeneity and supports the growing emphasis on personalized medicine in Parkinson's disease management[4, 6, 20].

Nevertheless, several limitations should be acknowledged. The included studies exhibited considerable heterogeneity in study design, sample size, age-at-onset definitions, follow-up duration, and reported clinical outcomes, limiting direct comparison across investigations. Furthermore, variations in diagnostic criteria and methodological approaches prevented quantitative data synthesis. Therefore, the findings of this review should be interpreted within the context of the available evidence, and future studies employing standardized definitions and multicentre prospective designs are warranted to strengthen the evidence base[25-27].

Future research should focus on identifying reliable biomarkers for early diagnosis, improving genotype-phenotype correlation, and developing precision medicine approaches tailored to different age-at-onset groups. Advances in molecular genetics, neuroimaging, artificial intelligence, and disease-modifying therapies may facilitate earlier diagnosis and more individualized therapeutic strategies. Longitudinal studies evaluating long-term clinical outcomes and cost-effectiveness of personalized treatment approaches are also required to improve patient care and optimize healthcare resource utilization[28-30].

Overall, the evidence synthesized in this systematic review demonstrates that EOPD and LOPD differ substantially in their biological basis, clinical phenotype, therapeutic response, and socioeconomic consequences. Recognition of these differences is essential for implementing age-specific diagnostic strategies, optimizing individualized treatment plans, and guiding future translational research aimed at improving the quality of life and long-term outcomes of patients with Parkinson's disease[4-30].

Bedside and Clinical Management Implications

Recognizing these distinct phenotypes has clear clinical implications for daily patient care:

In EOPD: First-line pharmacological strategies should focus on delaying motor complications by employing dopamine agonists, MAO-B inhibitors, or COMT inhibitors where appropriate, paired with regular screening for ICDs (compulsive gambling, shopping, and hypersexuality). When motor fluctuations become refractory, early evaluation for DBS or continuous infusion systems should be prioritized to preserve functional and vocational capacity.

In LOPD: Management should focus on conservative levodopa titration to maintain mobility while avoiding drug-induced hallucinations, orthostatic hypotension, and confusion. Physical therapy for balance and fall prevention, along with routine cognitive monitoring, should take precedence over aggressive motor escalation.

Study Limitations and Heterogeneity

Several limitations of the available literature should be noted. Considerable methodological heterogeneity exists across published studies regarding AAO cutoffs (ranging from 40 to 55 years), clinical rating scales, and follow-up durations, which limited quantitative meta-analysis across all outcomes. Furthermore, tertiary movement disorder centers introduce potential referral and publication biases by over-representing severe or genetically complex EOPD cases relative to population-based registries. Standardized AAO definitions and larger multi-center prospective registries are needed to resolve these disparities.

CONCLUSION

EOPD and LOPD represent clinically and biologically distinct phenotypes of Parkinson's disease. Age at onset serves as a key determinant of underlying genetic architecture, disease trajectory, and therapeutic response. While EOPD requires therapeutic strategies focused on managing motor complications, preserving vocational capacity, and offering targeted psychosocial support, LOPD necessitates careful pharmacological titration to mitigate cognitive decline, psychosis, and fall risks. Advancing precision medicine in PD will require standardized diagnostic cutoffs, validated biomarker discovery, and clinical trials stratified by age at onset.

DISCLOSURE

Funding: The authors received no specific financial support for this work.

Conflict of Interest: The authors declare that there are no conflicts of interest.

Ethical Approval: Not applicable. This systematic review was conducted using previously published literature and did not involve human participants or experimental animals.

ABBREVIATION

Abbreviation	Full Term / Definition
AAO	Age at Onset
ASDR	Age-Standardized Disability-Adjusted Life Years Rate
ASIR	Age-Standardized Incidence Rate
ASMR	Age-Standardized Mortality Rate
ASPR	Age-Standardized Prevalence Rate
COMT	Catechol-O-Methyltransferase
DALYs	Disability-Adjusted Life Years
DAs	Dopamine Agonists
DBS	Deep Brain Stimulation
***DJ-1* (*PARK7*)**	Protein Deglycase DJ-1 / Parkinson Disease Protein 7
EOPD	Early-Onset Parkinson's Disease
H&Y	Hoehn and Yahr (staging scale)
ICDs	Impulse Control Disorders
JBI	Joanna Briggs Institute
L-DOPA / Levodopa	L-3,4-Dihydroxyphenylalanine
LID	Levodopa-Induced Dyskinesia
LOPD	Late-Onset Parkinson's Disease
LRRK2	Leucine-Rich Repeat Kinase 2
MAO-B	Monoamine Oxidase B
MC	Motor Complications
MDS	International Parkinson and Movement Disorder Society
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Headings
MF	Motor Fluctuations
NMS	Non-Motor Symptoms
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
PD	Parkinson's Disease

Abbreviation	Full Term / Definition
PDQ-39	39-Item Parkinson's Disease Questionnaire
PICOS	Population, Intervention/Exposure, Comparator, Outcome, Study Design
PINK1	PTEN-Induced Kinase 1
PRKN* / *PARK2	Parkin RBR E3 Ubiquitin Protein Ligase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
SCOPA-COG	SCales for Outcomes in PArkinson's disease - COGnition
SDI	Socio-Demographic Index
SNCA	Synuclein Alpha
SNpc	Substantia Nigra pars compacta
UPDRS	Unified Parkinson's Disease Rating Scale
YOPD	Young-Onset Parkinson's Disease

References

1. Kalia LV, Lang AE. Parkinson's disease. *The Lancet*. 2015; 386 (9996) :896-912 . Available from: https://doi.org/10.1016/s0140-6736(14)61393-3
2. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, *et al*. Parkinson disease. *Nature Reviews Disease Primers*. 2017; 3 (1) . Available from: https://doi.org/10.1038/nrdp.2017.13
3. Bloem BR, Okun MS, Klein C. Parkinson's disease. *The Lancet*. 2021; 397 (10291) :2284-2303 . Available from: https://doi.org/10.1016/s0140-6736(21)00218-x
4. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *The Lancet Neurology*. 2006; 5 (6) :525-535 . Available from: https://doi.org/10.1016/s1474-4422(06)70471-9
5. Schrag A, Ben-Shlomo Y, Quinn NP. Cross sectional prevalence survey of idiopathic Parkinson's disease and parkinsonism in London. *BMJ*. 2000; 321 (7252) :21-22 . Available from: https://doi.org/10.1136/bmj.321.7252.21
6. Klein C, Westenberger A. Genetics of Parkinson's Disease. *Cold Spring Harbor Perspectives in Medicine*. 2012; 2 (1) :a008888 . Available from: https://doi.org/10.1101/cshperspect.a008888
7. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. *The Lancet Neurology*. 2020; 19 (2) :170-178 . Available from: https://doi.org/10.1016/s1474-4422(19)30287-x
8. Kasten M, Klein C. The many faces of genetic Parkinson's disease. *Journal of Neurochemistry*. 2013;125(4):494–501.
9. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. *Neuron*. 2003; 39 (6) :889-909 . Available from: https://doi.org/10.1016/s0896-6273(03)00568-3
10. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. *Nature Reviews Neuroscience*. 2017; 18 (2) :101-113 . Available from: https://doi.org/10.1038/nrn.2016.178
11. Schapira AHV, Jenner P. Etiology and pathogenesis of Parkinson's disease. *Movement Disorders*. 2011; 26 (6) :1049-1055 . Available from: https://doi.org/10.1002/mds.23732
12. Obeso JA, Stamelou M, Goetz CG, Poewe W, Lang AE, Weintraub D, *et al*. Past, present, and future of Parkinson's disease: A special essay on the 200th anniversary of the Shaking Palsy. *Movement Disorders*. 2017; 32 (9) :1264-1310 . Available from: https://doi.org/10.1002/mds.27115
13. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, *et al*. MDS clinical diagnostic criteria for Parkinson's disease. *Movement Disorders*. 2015; 30 (12) :1591-1601 . Available from: https://doi.org/10.1002/mds.26424
14. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease. *JAMA*. 2020; 323 (6) :548-560 . Available from: https://doi.org/10.1001/jama.2019.22360
15. Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K, *et al*. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Movement Disorders*. 2018; 33 (8) :1248-1266 . Available from: https://doi.org/10.1002/mds.27372
16. Connolly BS, Lang AE. Pharmacological Treatment of Parkinson Disease. *JAMA*. 2014; 311 (16) :1670-1683 . Available from: https://doi.org/10.1001/jama.2014.3654
17. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease (2009). *Neurology*. 2009; 72 (21_supplement_4) :S1-S136 . Available from: https://doi.org/10.1212/wnl.0b013e3181a1d44c
18. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A Five-Year Study of the Incidence of Dyskinesia in Patients with Early Parkinson's Disease Who Were Treated with Ropinirole or Levodopa. *New England Journal of Medicine*. 2000; 342 (20) :1484-1491 . Available from: https://doi.org/10.1056/nejm200005183422004
19. Schuepbach WMM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, *et al*. Neurostimulation for Parkinson's disease with early motor complications. *New England Journal of Medicine*. 2013; 368 (7) :610-622 . Available from: https://doi.org/10.1056/NEJMoa1205158
20. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, *et al*. A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease. *New England Journal of Medicine*. 2006; 355 (9) :896-908 . Available from: https://doi.org/10.1056/nejmoa060281
21. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, *et al*. Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease<subtitle>A Randomized Controlled Trial</subtitle>. *JAMA*. 2009; 301 (1) :63-73 . Available from: https://doi.org/10.1001/jama.2008.929
22. Marras C, Beck JC, Bower JH, Roberts E, Ritz B, Ross GW, *et al*. Prevalence of Parkinson's disease across North America. *npj Parkinson's Disease*. 2018; 4 (1) . Available from: https://doi.org/10.1038/s41531-018-0058-0
23. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Movement Disorders*. 2008; 23 (6) :837-844 . Available from: https://doi.org/10.1002/mds.21956
24. Wickremaratchi MM, Ben-Shlomo Y, Morris HR. The effect of onset age on the clinical features of Parkinson's disease. *European Journal of Neurology*. 2009; 16 (4) :450-456 . Available from: https://doi.org/10.1111/j.1468-1331.2008.02514.x

25. Mehanna R, Jankovic J. Young-onset Parkinson's disease: Its unique features and management. *Parkinsonism & Related Disorders*. 2019; 65 :39-48 . Available from: https://doi.org/10.1016/j.parkreldis.2019.06.001
26. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism & Related Disorders*. 2006; 12 (1) :35-41 . Available from: https://doi.org/10.1016/j.parkreldis.2005.06.011
27. Dorsey ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, *et al*. Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016. *BMJ*. 2019; :l94 . Available from: https://doi.org/10.1136/bmj.l94
28. Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. *Journal of Parkinson's Disease*. 2018; 8 (s1) :S3-S8 . Available from: https://doi.org/10.3233/jpd-181474
29. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. *The Lancet Neurology*. 2021; 20 (5) :385-397 . Available from: https://doi.org/10.1016/s1474-4422(21)00030-2
30. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry*. 2016; 139 (S1) :318-324 . Available from: https://doi.org/10.1111/jnc.13691