Focused Review
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Life Sciences, Medicine and Biomedicine

Overlapping pathological features of Alzheimer's and Parkinson's diseases: Clinical implications and future directions for improving diagnostic precision

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Received 19 August 2025; Revised 18 May 2026; Accepted 22 May 2026; Published online 26 July 2026

ABSTRACT

Alzheimer's disease (AD) and Parkinson's disease (PD) are two of the most common neurodegenerative disorders, each with distinct clinical and pathological features, yet sharing significant overlaps that complicate diagnosis and management. AD is primarily characterized by cognitive decline stemming from amyloid-beta plaques and tau tangles, while PD is defined by motor dysfunction caused by alpha-synuclein-containing Lewy bodies. Despite these differences, both diseases exhibit overlapping cognitive, neuropsychiatric, and motor symptoms, along with shared underlying mechanisms like neuroinflammation and abnormal protein aggregation. This article explores these overlapping features, including memory and executive function deficits, neuropsychiatric symptoms such as depression and apathy, and motor signs like bradykinesia and rigidity. It also discusses the diagnostic challenges arising from these overlaps, highlighting the limitations of current tools and the promise of a multi-modal diagnostic strategy that integrates clinical evaluation, advanced neuroimaging, and emerging biomarkers. The review concludes by outlining future research directions, emphasizing the potential of advanced imaging, early detection of dual pathologies, and the development of integrated therapeutic approaches to enable precision medicine for these complex disorders.

Keywords: *Alzheimer's disease; Parkinson's disease; dementia; neurodegeneration and pathology*

INTRODUCTION

Overview of Alzheimer's disease and Parkinson's disease

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common age-related neurodegenerative disorders, but they are not simply mirror images of memory-first and motor-first decline (Perl et al., 1998). AD is primarily associated with extracellular amyloid-beta deposition, intracellular hyperphosphorylated tau, progressive synaptic dysfunction, and hippocampal-cortical neurodegeneration, whereas PD is defined by alpha-synuclein aggregation, Lewy body formation, and degeneration of dopaminergic neurons in the substantia nigra that disrupts basal ganglia circuitry (Cantone & Sacco, 2023; Perl et al., 1998).

These canonical distinctions remain clinically useful: early episodic memory loss, spatial disorientation, and aphasia favor AD, while asymmetric bradykinesia, resting tremor, rigidity, and postural instability favor PD (Cantone & Sacco, 2023). Nevertheless, symptom boundaries blur over time. Many patients with PD develop cognitive impairment or dementia, and some patients with AD later show parkinsonian motor features, particularly gait slowing and rigidity (Perl et al., 1998). This overlap is even more pronounced when related syndromes such as Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are considered (McKeith et al., 2017).

From a clinical standpoint, the key issue is not merely that AD and PD share symptoms, but that the timing, pattern, and biological context of those symptoms differ (Perl et al., 1998). Recognizing those distinctions is essential because

https://doi.org/10.28916/lsmb.10.1.2026.213

diagnostic misclassification may alter counseling, prognosis, medication choice, and eligibility for biomarker-based studies or disease-modifying trials (McKeith et al., 2017). This review therefore focuses on both overlap and differentiation, rather than treating shared symptoms as evidence that the disorders are identical (Perl et al., 1998).

Overlapping clinical symptoms and features that help differentiate AD, PD, PDD, and DLB

Cognitive impairment

Both AD and PD can impair cognition, but the dominant profile differs. In typical AD, episodic memory impairment appears early because medial temporal lobe networks are affected early in the disease course (Pleizier et al., 2012). Deficits in new learning, delayed recall, word finding, and spatial navigation therefore tend to be prominent at presentation (Bronnick et al., 2007). By contrast, early cognitive changes in PD more often involve executive dysfunction, slowed processing speed, reduced set shifting, and impaired attention, reflecting frontostriatal dysfunction rather than a primary amnestic syndrome (Crowley et al., 2021).

This distinction matters diagnostically. Patients with PD who mainly show executive dysfunction may be mislabeled as having AD if cognitive screening relies too heavily on global scores and does not profile domain-specific deficits (Bronnick et al., 2007). Conversely, a patient with AD who develops psychomotor slowing may be mistaken for having a synucleinopathy if the memory-led onset is not carefully documented (Andrade-Guerrero et al., 2024). In later disease stages, however, cognitive phenotypes can converge, especially in PDD and DLB, where visuospatial and attentional deficits may coexist with memory impairment.

The chronology of dementia is particularly important. In PDD, established Parkinsonism precedes dementia by more than one year, whereas in DLB, dementia occurs before, concurrently with, or within one year of Parkinsonian motor signs. In contrast, dementia in AD usually precedes substantial parkinsonism, and when motor findings do occur, they are often milder, less asymmetric, and less tremor-dominant than in idiopathic PD. This “1-year rule” is imperfect, but it remains a practical clinical convention for differentiating PDD from DLB (McKeith et al., 2017).

Neuropsychiatric symptoms

Depression, anxiety, apathy, sleep disruption, hallucinations, and delusions are common across the AD–PD spectrum, but their clinical implications differ. Depression and apathy are frequent in both disorders and are associated with poorer daily functioning, faster disability, and increased caregiver burden (Kang et al., 2014; Lawrence et al., 2014). In PD, apathy and depression may arise from dopaminergic and frontostriatal dysfunction, whereas in AD they often coexist with progressive cortical-limbic degeneration (Chung et al., 2016).

Hallucinations provide a useful differentiating clue. Visual hallucinations can occur in advanced AD (Luca et al., 2026), but recurrent, well-formed visual hallucinations early in the disease course are more characteristic of DLB and may also appear in PD, especially with advancing disease or dopaminergic treatment exposure. REM sleep behavior disorder (RBD) also helps differentiation: it strongly supports a synucleinopathy such as PD or DLB and is not a defining feature of typical AD (Chan et al., 2018).

These overlaps affect treatment decisions. Increasing dopaminergic therapy may improve mobility in PD but can worsen hallucinations or confusion (Wang et al., 2023); conversely, emphasizing cholinesterase-based treatment for presumed AD may provide limited benefit if the dominant syndrome is a motor-first synucleinopathy (Sharma et al., 2019). Thus, neuropsychiatric overlap is not just descriptive; it changes risk-benefit calculations in everyday care.

Motor symptoms

Motor overlap also requires careful interpretation. Bradykinesia and rigidity are cardinal signs of PD and usually arise from nigrostriatal dopaminergic depletion. Their classical pattern includes asymmetry at onset, reduced arm swing, decrementing repetitive movements, and in many cases a resting tremor (Bloem et al., 2021). In AD, by contrast, motor slowing, and gait disturbance tend to emerge later and are more often linked to impaired motor planning, visuospatial dysfunction, frailty, or mixed pathology rather than primary basal ganglia degeneration (Andrade-Guerrero et al., 2024).

Several motor clues can therefore help distinguish the disorders. Resting tremor, marked asymmetry, clear levodopa responsiveness, and preceding hyposmia or RBD favor PD (Bloem et al., 2021). Early severe episodic memory loss with only mild symmetric gait slowing favors AD (Ozkan et al., 2023). DLB occupies an intermediate clinical position, with dementia plus fluctuating cognition, hallucinations, and spontaneous Parkinsonism (McKeith et al., 2017). Because late-stage AD, PD, PDD, and DLB may all present with falls, freezing, rigidity, and cognitive impairment, clinicians should interpret motor signs within the broader time course rather than in isolation.

Shared mechanisms, dual proteinopathies, and prognostic implications

The overlap between AD and PD is also biological. Mixed pathology is common in older adults, and neuropathological studies show that tau, amyloid-beta, and alpha-synuclein frequently coexist rather than remaining confined to one “pure” disease category (Mohan Kumar & Talwar, 2025). This is clinically relevant because dual proteinopathies are often associated with greater cognitive burden, more complex symptom profiles, and less predictable progression than single-pathology cases.

Mechanistically, these proteins may interact rather than accumulate independently. Experimental and translational studies suggest cross-seeding, impaired proteostasis, mitochondrial stress, lysosomal dysfunction, and chronic glial activation may amplify each other across disease pathways (Kim et al., 2024; Röntgen et al., 2025). Neuroinflammation is especially important because activated microglia and astrocytes can both respond to and further propagate protein aggregation, synaptic dysfunction, and neuronal injury (Detka et al., 2024).

These shared mechanisms help explain why patients with PD who also harbor AD-type pathology often have faster cognitive decline, and why patients with AD who accumulate Lewy bodies may show hallucinations, visuospatial dysfunction, or Parkinsonism. They also affect biomarker interpretation. For example, amyloid or tau positivity in a patient with PD may indicate concomitant AD-type pathology rather than “typical” PD alone, and reduced CSF alpha-synuclein is not by itself sufficient to distinguish all synucleinopathy subtypes with confidence (Alves et al., 2010; Angel Pinto et al., 2026).

From a prognostic perspective, dual pathology generally suggests a more heterogeneous and potentially less favorable course, particularly for cognition. This is one reason why purely symptom-based diagnostic labels can be inadequate. A patient categorized clinically as PD may have substantial AD co-pathology that changes expected progression, while a patient labeled as AD may have Lewy-related pathology that increases the risk of hallucinations, fluctuating attention, and sensitivity to certain medications.

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Biomarkers and diagnostic differentiation: What helps, and what remains limited?

No single test can fully separate AD, PD, PDD, and DLB in all settings, so diagnosis still depends on integrating clinical chronology with targeted investigations. In AD, the most established supportive biomarkers are amyloid and tau measures from cerebrospinal fluid (CSF) or amyloid/tau positron emission tomography (PET), together with structural MRI evidence of medial temporal and temporoparietal atrophy (Jack et al., 2024). In PD, dopamine-transporter imaging and neuromelanin-sensitive MRI can support nigrostriatal degeneration, while clinical response to dopaminergic therapy remains a practical part of assessment (Okitsu et al., 2023).

The usefulness of these tools varies by question asked. Amyloid and tau biomarkers are valuable for identifying AD-type pathology, but they do not rule out coexisting synucleinopathy. Conversely, dopamine-transporter deficits support a Parkinsonian syndrome but do not by themselves distinguish PD from DLB. CSF alpha-synuclein and related assays remain promising, yet methodological variability and limited standardization currently restrict broad clinical adoption (Mohan Kumar & Talwar, 2025).

Imaging must also be interpreted critically. MRI and PET improve diagnostic confidence, but access is uneven, costs are substantial, and sensitivity may be lower in prodromal or mixed-pathology states. Molecular imaging can clarify pathology, yet it is not universally available and may not be feasible for all patients because of financial, geographic, or comorbidity constraints. Blood-based biomarkers are an important frontier because they could increase accessibility, but their role in routine differentiation between AD and synucleinopathy-spectrum disorders is still evolving.

In practical terms, some tests are more informative within specific clinical categories. Marked amyloid/tau positivity supports AD-type biology in a patient with early memory loss. A history of RBD, recurrent visual hallucinations, cognitive fluctuations, and abnormal dopamine-transporter imaging supports DLB (Chan et al., 2018). Long-standing PD followed by later dementia supports PDD. However, because overlap and comorbidity are common, clinicians should avoid overconfidence when biomarker findings and symptom chronology point in different directions (McKeith et al., 2017).

Variability of prevalence estimates, limitations of current evidence, and research gaps

Reported prevalence estimates for overlapping symptoms vary widely across studies, and this variability is itself important. Differences in study setting, disease stage, referral patterns, diagnostic criteria, cognitive instruments, and inclusion of mixed-pathology cases all influence reported rates of depression, apathy, hallucinations, executive dysfunction, and Parkinsonism (Pagonabarraga et al., 2023). As a result, prevalence figures should be interpreted as context-dependent rather than universal.

The existing literature also has several methodological limitations. First, many studies are cross-sectional and therefore describe coexistence of symptoms without clarifying temporal order or causal direction. Second, clinic-based cohorts may overrepresent more complex or advanced cases, inflating estimates of overlap. Third, biomarkers are not

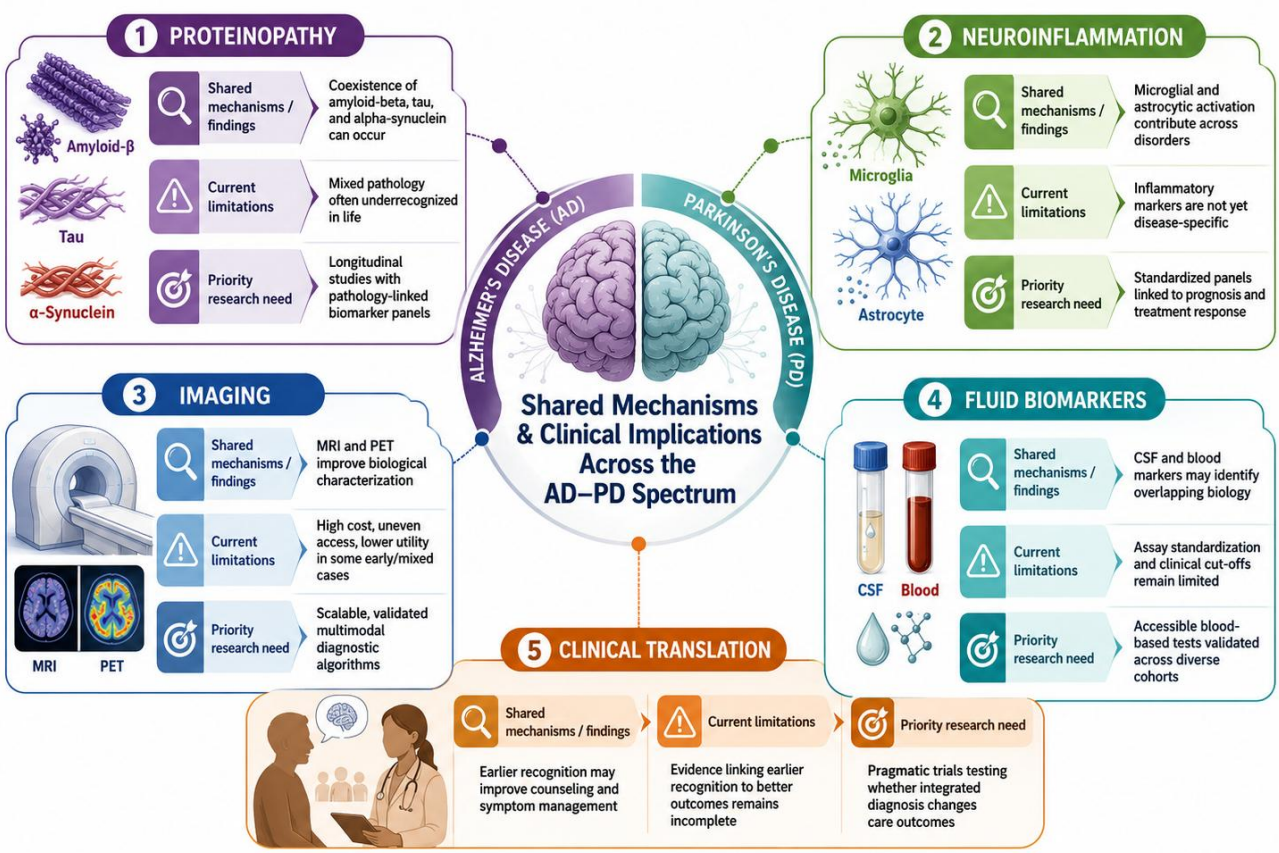
consistently applied across studies, so “AD” and “PD” groups may unknowingly include mixed-pathology participants. Fourth, older adults with multimorbidity are often excluded from tightly controlled studies even though they are the group most likely to exhibit overlapping syndromes in practice.

Another limitation is imbalance in the evidence base. Cognitive and neuropsychiatric overlap is discussed extensively, but fewer studies directly test how these overlaps change treatment response, prognosis, or cost-effectiveness of biomarker use in real-world care. Similarly, many emerging biomarker and machine-learning studies remain promising but not yet mature enough for widespread clinical implementation because of limited external validation, assay standardization, and accessibility (Aborode et al., 2025; Ou et al., 2021).

Future studies should therefore use harmonized diagnostic criteria, longitudinal designs, mixed-modality biomarker panels, and more explicit characterization of co-pathology. Research should also move beyond classification alone and ask whether early identification of these overlaps changes management, caregiver burden, hospitalization, institutionalization, or response to targeted therapy (Figure 1).

Figure 1

Summary of shared versus distinct mechanisms and clinical implications across the AD–PD spectrum



Impact on patient care and treatment selection

Overlapping syndromes complicate patient care at every stage. Diagnostic uncertainty can delay counseling, defer symptomatic treatment, and make families uncertain about prognosis. It also increases the risk of prescribing decisions that improve one domain while worsening another. For example, escalating dopaminergic therapy may relieve bradykinesia but aggravate psychosis, whereas sedating antipsychotic strategies may worsen mobility and cognition in vulnerable patients (Husa et al., 2014; Wolters, 1999).

A structured, multidisciplinary approach is therefore essential. Clinical management should incorporate neurology, geriatrics, neuropsychology, psychiatry, rehabilitation, and caregiver education. The most useful framework is often not “AD versus PD” in isolation, but rather an individualized formulation of dominant symptoms, likely biology, medication sensitivities, safety risks, and anticipated trajectory. This approach is particularly important in DLB and mixed-pathology states, where visual hallucinations, fluctuations, falls, and autonomic symptoms may coexist with memory decline.

Importantly, recognizing overlap may improve outcomes even before disease-modifying therapies become available. Early identification of hallucination risk, sleep disorders, executive impairment, and gait instability can guide safer prescribing, fall prevention, driving assessment, caregiver planning, and tailored cognitive or physical

rehabilitation. Table 1 summarizes the most clinically useful points of distinction and overlap across AD, PD, PDD, and DLB.

Table 1

Practical differentiation and overlap across AD, PD, PDD, and DLB

Feature	AD	PD	PDD	DLB	Clinical value for differentiation
Typical onset pattern	Memory-led cognitive decline	Motor-led syndrome	Established PD followed by later dementia	Dementia before, with, or within 1 year of Parkinsonism	Chronology remains one of the most useful bedside clues
Dominant early cognition	Episodic memory, language, orientation	Executive dysfunction, attention, bradyphrenia	Executive + visuospatial deficits after PD onset	Attention, visuospatial dysfunction, fluctuations	Domain profile helps interpret low screening scores
Motor phenotype	Late, milder Parkinsonism may occur	Asymmetric bradykinesia, rigidity, tremor	Parkinsonism already established	Spontaneous Parkinsonism, often less classic than PD	Asymmetry, tremor, and levodopa response favor PD-spectrum disease
Hallucinations/ fluctuations	Usually later	May occur later or with medication	Common as disease advances	Core feature	Early recurrent visual hallucinations strongly suggest DLB
Helpful biomarkers	Amyloid/tau CSF or PET; MRI atrophy	DaT imaging; supportive MRI; clinical response	PD chronology + supportive biomarkers	DaT imaging + core clinical features	Biomarkers support but do not replace chronology and examination

Note: AD: Alzheimer's disease; PD: Parkinson's disease; PDD: Parkinson's disease dementia; DLB: dementia with Lewy bodies; CSF: cerebrospinal fluid; PET: positron emission tomography and MRI: magnetic resonance imaging.

Future research directions

Future research should prioritize clinically actionable multimodal models rather than isolated biomarkers. Combining symptom chronology, neuropsychological profiling, structural and molecular imaging, and scalable fluid biomarkers may improve diagnostic accuracy more than any single modality alone (Nakaoku et al., 2025).

In addition to improving diagnosis, future work should explore biology-informed intervention strategies that target shared mechanisms across the AD–PD spectrum. One potential future avenue is pharmacological preconditioning, a strategy initially and extensively investigated in stroke and neurodegenerative models (Nik Ramli & Siran, 2015), whereby low-dose or controlled pharmacological stimuli are used to activate endogenous protective pathways and enhance neuronal resilience before irreversible injury or degeneration occurs (Nik Ramli et al., 2015). Microglial preconditioning in AD has been proposed to recalibrate maladaptive neuroinflammatory responses, while exercise preconditioning in MPTP-induced Parkinsonian mice has been shown to improve motor deficits by enhancing mitochondrial function. These findings support future exploration of pharmacological or lifestyle-based preconditioning to strengthen glial, mitochondrial, oxidative stress, and neurotrophic resilience, although optimal timing, safety, durability, and patient selection require careful validation (Xu et al., 2025; Yassaghi et al., 2024).

Finally, future work should evaluate whether integrated diagnostic approaches are practical and equitable (Table 2). A diagnostically sophisticated model is only useful if it can be implemented beyond major tertiary centers. Cost, assay standardization, workforce training, and global access must therefore be considered alongside scientific validity.

Table 2

Summary of shared versus distinct mechanisms and clinical implications across the AD–PD spectrum

Domain	Shared mechanisms/ findings	Current limitations	Priority research need
Proteinopathy	Coexistence of amyloid-beta, tau, and alpha-synuclein can occur	Mixed pathology often underrecognized in life	Longitudinal studies with pathology-linked biomarker panels
Neuroinflammation	Microglial and astrocytic activation contribute across disorders	Inflammatory markers are not yet disease-specific	Standardized panels linked to prognosis and treatment response
Imaging	MRI and PET improve biological characterization	High cost, uneven access, lower utility in some early/mixed cases	Scalable, validated multimodal diagnostic algorithms
Fluid biomarkers	CSF and blood markers may identify overlapping biology	Assay standardization and clinical cut-offs remain limited	Accessible blood-based tests validated across diverse cohorts
Clinical translation	Earlier recognition may improve counseling and symptom management	Evidence linking earlier recognition to better outcomes remains incomplete	Pragmatic trials testing whether integrated diagnosis changes care outcomes

CONCLUSION

AD and PD share substantial cognitive, neuropsychiatric, motor, and biological overlap, but the differences in symptom chronology, dominant cognitive pattern, motor phenotype, and biomarker profile remain clinically meaningful. Distinguishing AD, PD, PDD, and DLB requires more than listing shared symptoms; it requires attention to when symptoms emerge, how they cluster, and which biomarkers support or challenge the initial clinical impression. Mixed proteinopathies and neuroinflammatory mechanisms further complicate these boundaries and help explain why prognosis is often more heterogeneous than traditional labels suggest.

Accordingly, the most informative clinical strategy is a multimodal and longitudinal one. By integrating careful bedside assessment with appropriate imaging and biomarker tools, clinicians can better navigate overlap, reduce misdiagnosis, and move toward more individualized care for patients across the neurodegenerative spectrum. These advances also align with Sustainable Development Goal 3 (SDG3: Good Health and Well-Being) by supporting improved diagnosis and clinical management of neurodegenerative disorders and promoting healthier ageing.

AUTHOR CONTRIBUTIONS

The study was conceptualised and designed by Nur Batrisyia Nizam and Muhammad Danial Che Ramli. Resource acquisition was carried out by Nur Batrisyia Nizam and Nur Athirah Azlan. The manuscript was reviewed by Nik Nasihah Nik Ramli and Muhammad Danial Che Ramli. Final approval of the manuscript was done by Nik Nasihah Nik Ramli.

ETHICS APPROVAL

Not applicable.

FUNDING

This article was funded by the Management and Science University.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Not applicable.

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Citation:

Nizam, N. B., Nik Ramli, N. N., Azlan, N. A., & Che Ramli, M. D. (2026). Overlapping pathological features of Alzheimer's and Parkinson's diseases: Clinical implications and future directions for improving diagnostic precision. *Life Sciences, Medicine and Biomedicine, 10(1).*

https://doi.org/10.28916/lsmb.10.1.2026.213

Life Sciences, Medicine and Biomedicine
ISSN: 2600-7207