# Parkinsonian Dementia: Diagnosis, Differentiation and Principles of Treatment

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The terms parkinsonism and Parkinson syndrome (PS) are used interchangeably. Two of the three cardinal features—bradykinesia, rigidity and tremor—are necessary to make a diagnosis of PS. Several pathological entities and neuroleptic drugs may produce PS, the most common being Parkinson's disease or idiopathic Parkinson's disease (PD), which is characterized by marked neuronal loss in the substantia nigra and Lewy body (LB) inclusions (Figure 1). The prevalence of PS in the Canadian general population is estimated at 300 per 100,000.[1] The mean age of onset is 62 years, with both incidence and prevalence rates increasing with age. In a Canadian survey of a community population over age 65 years, 3% had PS.[2]

Alzheimer disease (AD) is the most common dementing illness in the industrialized countries. Marked cortical neuronal loss, plaques and intraneuronal neurofibrillary tangles are pathological features of AD (Figure 2A and 2B). More than 5% of the general population over 65 years of age have AD.

Because both PD and AD occur in old age, some individuals will have both. Pathological studies suggest that this overlap is higher than expected in unselected large autopsy series.

## Classification of Dementia in PS

There are three main subgroups of dementia in PS:

I. Incidental dementia. This includes: multi-infarct dementia, hypothyroidism, B12 deficiency, folate deficiency, hypercalcemia, recurrent hypoglycemia, B1 deficiency, normal pressure hydrocephalus and others. While the other causes manifest with expected frequency, multi-infarct dementia is less common in PD.[3]

II. Parkinson variants where dementia is characteristic or a common feature. These include Creutzfeldt-Jacob disease, Pick's disease, corticobasal

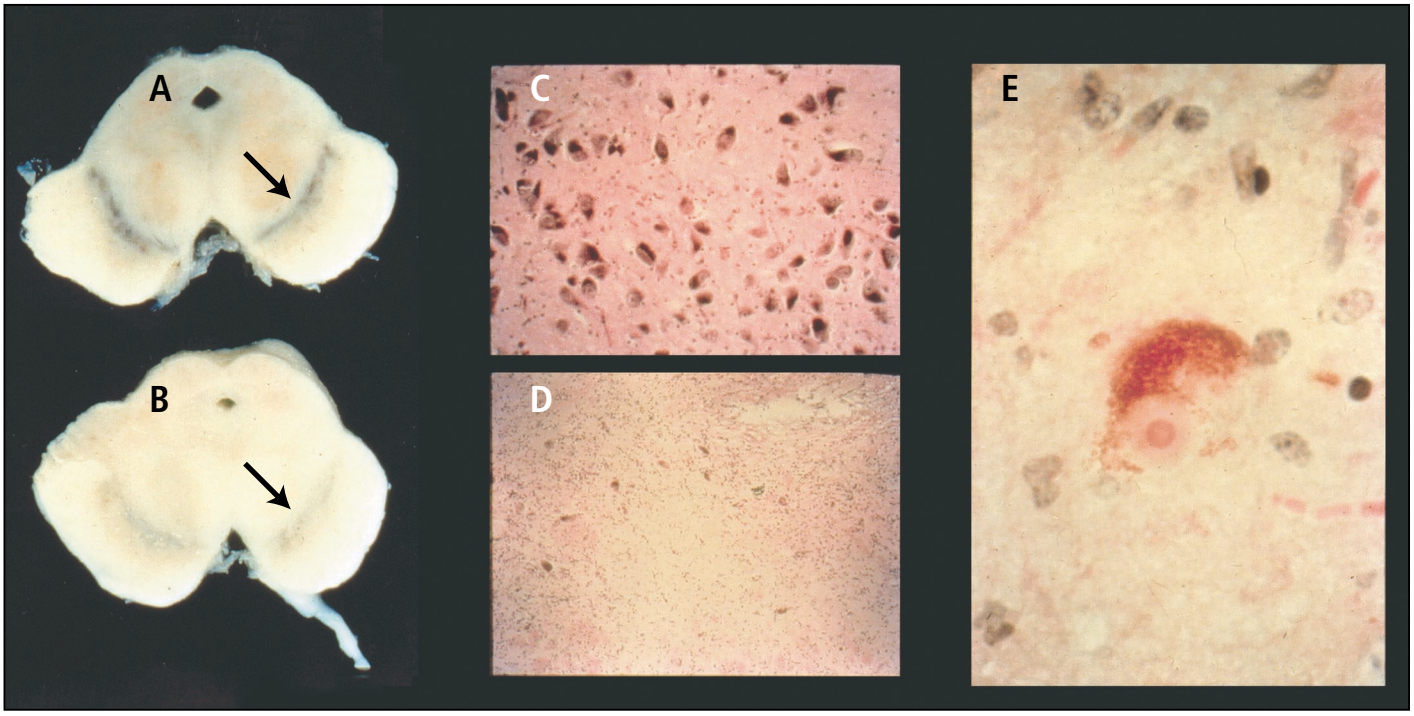



**Figure 1:** In the left and middle sets of photographs, the control brain substantia nigra (SN) is above and Parkinson's Disease SN is below.
Gross pathology (left)—contrast the dark stripe of SN above (A) with the pale appearing SN below (B).
Microscopic view (middle)—note the abundant pigmented neurons above (C) compared with neuronal loss and gliosis below (D).
Lewy body inclusions (right)—eosinophilic inclusion surrounded by a 'halo' in a melanin-containing neuron (E).

ganglionic degeneration, progressive supranuclear palsy and rare genetic variants.

III. Dementia in Parkinson's disease.

At any given point, if all the community PD patients were evaluated, between 11–30% would have dementia.[4-7] When compared to age-matched subjects, non-demented PD patients are more likely to develop dementia eventually. Prospective studies noted that, during a five-year follow-up, there is four to six times higher frequency of dementia in the PD cases, relative to the controls.[8-10] Onset in old age, advanced motor disability and male sex increase the risk of dementia in PD.[10,11] Although dementia is more common than expected, most PD patients do not have dementia, even at advanced stages of the illness. On levodopa treatment, the life expectancy in PD patients has increased substantially.[12] However, dementia is not caused by levodopa therapy.[13] Patients taking anticholinergics may exhibit reversible confusion resembling dementia.

There are two main dementia variants attributable to the underlying pathology in PD: subcortical and cortical.

The major neuropathology in PD is subcortical (Figure 1). Involvement of the basal nucleus basalis of Meynert is believed to be critical for subcortical dementia. These patients have slowed thought processes, but with cues, can retrieve information. They are often apathetic, indecisive and have impaired motivation and arousal. The subcortical dementia entity is controversial,[14] as there is no clinicopathological series to substantiate it. However, some patients present with that clinical picture.

The second variant is cortical dementia. Figure 1 represents the most common site of pathology in PD. In recent years, it has been recognized that additional LB pathology can be present in the cerebral cortex. When these changes are pronounced, they manifest as dementia. These patients also have some Alzheimer-like changes: prominent plaques but not neuronal tangles.[15,16] Standard staining methods used in the past did not identify the cortical LB and these cases were often diagnosed as AD or as "cause unknown." Newly developed immunohistochemical staining for ubiquitin and α-synuclein allow better identification of cortical LB.[15,17] Because of the overlapping pathology of PD and AD, several different terms have been used including senile dementia of LB type, dementia associated with cortical LB, diffuse LB disease and LB variant of AD.[16] The current terminology is dementia with Lewy bodies (DLB), which accounts for 15–25% of all autopsy studied dementia cases and is second only to AD.[16]

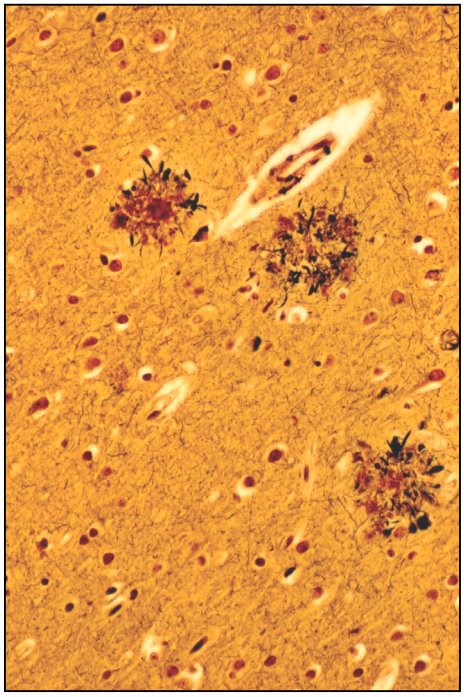


**Figure 2A:** Amyloid plaques (extracellular) seen in Alzheimer disease

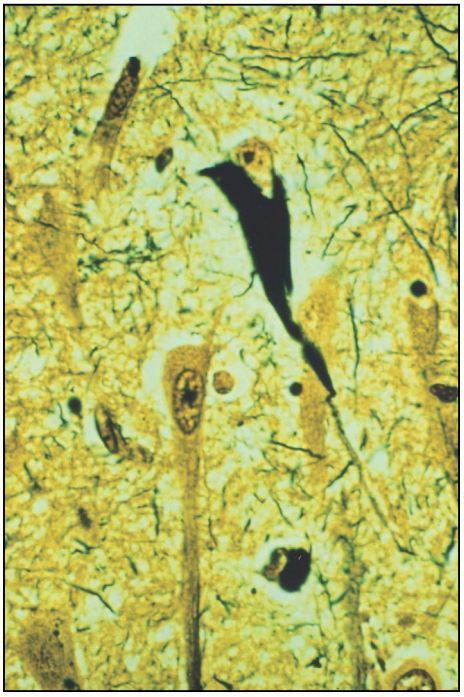


**Figure 2B:** Neurofibrillary tangle (intraneuronal) seen in Alzheimer disease

The pathophysiology of DLB is not fully understood. Widespread LB inclusions are seen in the limbic cortex and in the neo-cortex, but the severity of dementia may not always correlate with the severity of pathology.[15] The biochemical basis of the dementia is believed to be reduced cholineacetyltransferase (ChAT) activity in the frontal and the hippocampal areas resulting in cholinergic dysfunction.[18]

The primary clinical features of DLB are dementia, parkinsonian motor features and prominent visual hallucinations. Other common manifestations are delusions, cognitive fluctuations (variations from hour to hour or day to day) and episodic delirium. The cognitive switches may be sudden, from near normal to significantly impaired status. Most DLB cases have spontaneous parkinsonian features. DLB cases are highly sensitive to dopamine blocking neuroleptic drugs. A small dose of such agents (e.g. haloperidol) would accentuate PS,[16] and the enhanced motor disability may not remit after stopping the drug. The first manifestation may be parkinsonism and, usually within one year, there is dementia. Alternatively, some individuals may have onset as dementia indicating that cortical pathology may begin before the subcortical pathology.[15] Some AD patients may also develop parkinsonian features, notably bradykinesia and rigidity. Consequently the clinical distinction between DLB and AD may be difficult. In most reports, DLB is underdiagnosed—up to 55% of cases may not be clinically diagnosed accurately.[15,19]

The only laboratory test that can distinguish between AD and DLB is the fluorodopa PET scan—reduced fluorodopa striatal uptake being a feature of DLB.[20]

**Table 1**
**Differentiation between Lewy Body Dementia and Alzheimer Disease**

| | Dementia with Lewy Bodies | Alzheimer Disease |
|---|---|---|
| **Mode of Onset** | Parkinsonism and within one yr dementia, dementia at onset or both simultaneously. | Dementia beginning with memory impairment. Aphasia, agnosia and apraxia common. |
| **Course** | Progressive worsening of parkinsonian manifestations (tremor, bradykinesia, rigidity) and dementia. | Progressive worsening of dementia. Mild bradykinesia and rigidity in some patients—usually no tremor. |
| **Biochemical abnormalities** | Pronounced striatal dopamine deficiency and subcortical cholinergic deficiency. | Reduced synthesis of acetylcholine in several brain areas—cortical cholinergic deficiency. |
| **Falls** | Common and prominent feature. | Less common. |
| **Dysphagia and dysarthria** | More common. | Less common. |
| **Language difficulty** | Less severe. | Pronounced. |
| **Neuroleptic drug sensitivity** | Highly sensitive—develop adverse effects on small dose. | Not characteristic. |
| **Fluctuating state of cognitive function from hour to hour or day to day** | Present. | Present. |
| **Life Expectancy** | Shortened. | Shortened and especially so if there are extrapyramidal symptoms. |
| **Response to antiparkinsonian drugs** | Good early response. After onset of dementia, response poor and psychiatric adverse effects common. | Bradykinesia and rigidity do not respond to antiparkinsonian drugs. |
| **Response to anticholinesterase agents** | Mild (may worsen parkinsonism). | Mild improvement. |
| **Apolipoprotein allele** | ApoE ε4 allele does not increase risk. | ApoE ε4 allele increases risk. |
| **Fluorodopa PET Scan** | Reduced basal ganglia uptake indicating nigrostriatal pathology. | Normal uptake. |

PET scan is not accessible for standard patient care. ApoE ε4 allele, which is associated with an increased risk of AD, does not influence the risk of DLB.[21,22] Testing for the ε4 allele is of little use clinically. Table 1 shows the clinical and laboratory investigations helpful in distinguishing between AD and DLB.

## Principles of Treatment

Pharmacologic therapy is aimed at: 1) improving cognitive function; and 2) controlling psychiatric and behaviour problems.

The two special considerations are:

1. DLB patients should not be treated with classical neuroleptic agents.
2. Most DLB patients have significant parkinsonism which needs treatment.

The antiparkinsonian drug of choice in these patients is levodopa (Prolopa or Sinemet). Compared to the non-demented PD patient, DLB patients are more likely to develop hallucinations on levodopa.

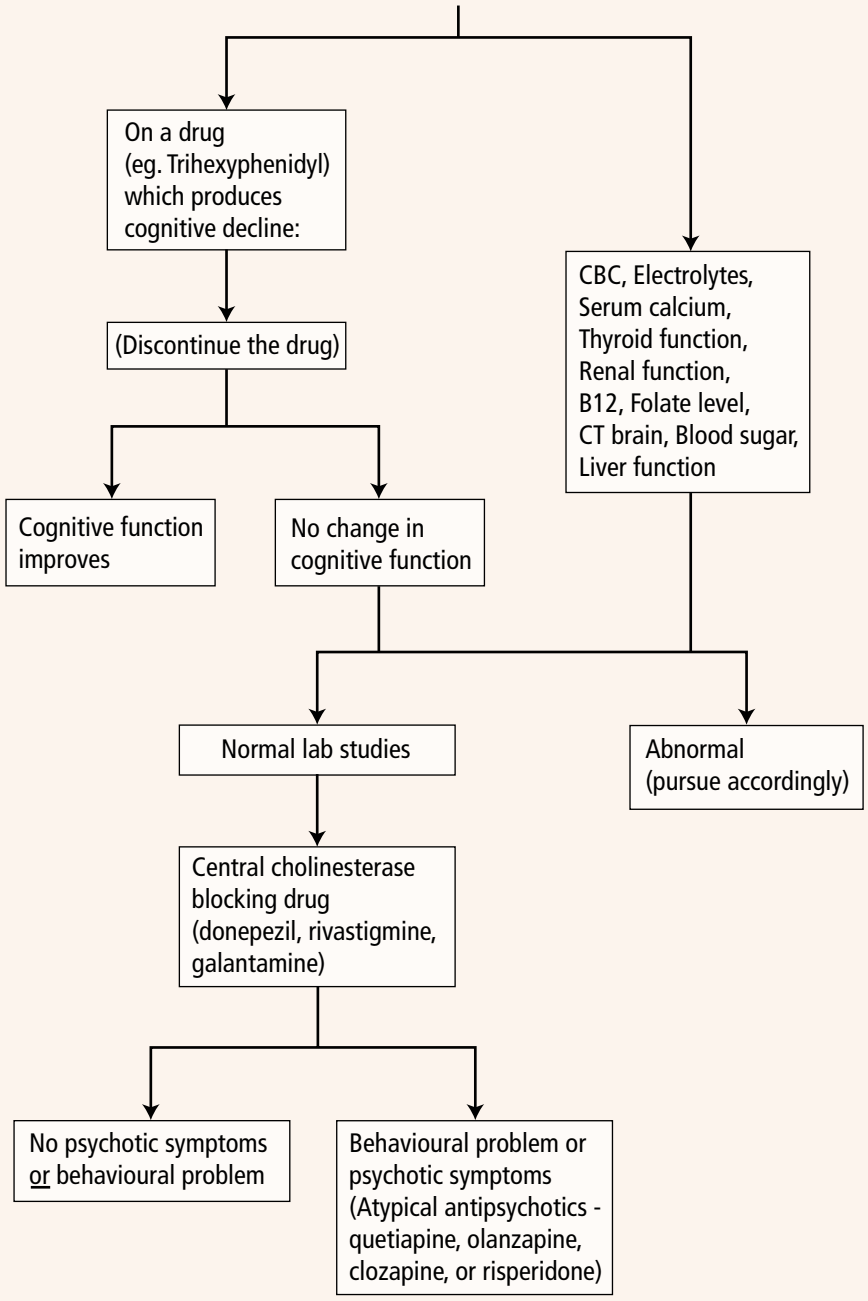
Similar to AD, the biochemical basis of dementia in DLB is believed to be cortical cholinergic deficit; therefore, the treatment is similar. There is a theoretical possibility that drugs that enhance central cholinergic activity may worsen parkinsonism. Based on clinical trials and observations by many experts this has not occurred. The drugs aimed at improving cognitive function are centrally acting cholinesterase inhibitors (donepezil, rivastigmine and galantamine). Donepezil (Aricept) is a pure acetylcholinesterase inhibitor and is given as 5 mg or 10 mg OD. Rivastigmine (Exelon) is a reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase.[23] The daily dose range is 3–12 mg. The usual maintenance dose is

6–12 mg in two divided doses. There is evidence suggesting that butyrylcholinesterase may be involved in transforming amyloid precursor proteins into amyloid β-proteins which are deposited in plaques.[24] Galantamine (Reminyl) inhibits acetylcholinesterase and causes allosteric modulation of presynaptic nicotinic receptors. This modulation results in increased release of, and response to, acetylcholine.[25,26] The total daily dose is 16–24 mg given in two divided doses.[27] All these drugs are known to be effective in mild to moderate AD.

In one study of demented PD cases (baseline MMSE: 20.7), donepezil produced a significant increase in MMSE score (i.e. 2.1 points) without worsening parkinsonism.[28] In a double-blind placebo controlled study of DLB patients, rivastigmine improved cognitive function and behavioural aspects, including delusions and hallucinations.[29] The initial treatment should be to use one of these agents alone. If the behavioural or psychiatric manifestations persist, an antipsychotic agent may be added (see flow chart in Figure 3).

The use of dopamine blocking antipsychotic agents is not recommended, as they may worsen PS. Instead, the newer atypical antipsychotic agents are used. There are four atypical antipsychotic drugs: clozapine (Clozaril), quetiapine (Seroquel), olanzapine (Zyprexa) and risperidone (Risperdal). Based on the consideration of parkinsonian manifestations, the drug of choice is clozapine. However, it produces agranulocytosis and patients need close monitoring. The company has recently sent out letters to all physicians warning of an increased risk of myocarditis, especially in the first month of treatment on clozapine. The second choice from that perspective (i.e. PS features) is quetiapine, though some worsening of parkinsonism has been reported. The third choice is olanzapine, which may also worsen parkinsonism. Risperidone in excess of 1 mg a day is most likely to worsen PS. Recently, these drugs were extensively reviewed.[30] The doses used for PD are much lower than for schizophrenia.

**Figure 3: Investigation and Management of the Parkinsonian Patient with Dementia**




Other support for safety and to facilitate orientation and to surroundings

In addition to pharmacological agents, these patients will need appropriate environments for safety, easy routines to follow, and external cues to help orientation and prevention of confusion.

## Summary

Parkinson syndrome (PS) includes several pathological entities, the most common being the idiopathic Parkinson's Disease (PD). PD is characterized by marked substantia nigra neuronal loss and neuronal Lewy body inclusions. Some uncommon PS variants have dementia as part of the clinical picture. If all PD patients in a community were evaluated at the same time, between 11–30% would have clinically recognizable dementia. At one time,

it was believed that PD pathology was restricted to the subcortical nuclei and dementia was consequent to that. More recent studies indicate that a proportion of the PD cases may also have large numbers of Lewy body inclusions in the cortical neurons and associated dementia. Such cases are known as dementia with Lewy bodies (DLB). It is now believed that DLB is second in frequency only to Alzheimer disease as the degenerative cause of dementia. Typically, the DLB cases have parkinsonism and early in the course develop dementia. These patients tolerate the standard dopamine blocking neuroleptic agents poorly and are more prone to psychiatric adverse effects on antiparkinsonian drugs. Some Alzheimer disease patients may also have clinical features of PS – akinesia and rigidity. This coexistence of dementia and PS in the two disorders makes clinical distinction between AD and DLB difficult. However, all these patients are best treated with atypical antipsychotic agents where necessary, may benefit from drugs aimed at cognitive improvement used in Alzheimer disease—donepezil, rivastigime, and galantamine—and their parkinsonian features respond best to levodopa. ◆

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