

Targeted Therapies in Parkinson's Disease

Treating Parkinson's Disease: The Pharmacist's Role

James Parkinson's 1817 "Essay on the Shaking Palsy,"^{1,2} we have learned that patients with Parkinson's disease (PD) lose cells in the substantia nigra, and striatum dopamine concentrations are markedly decreased. Arvid Carlsson, ML, MD, earned the Nobel Prize for Medicine in 2000 for his trials of levodopa in PD patients.³ Researchers have identified genetic mutations, abnormal handling of misfolded proteins by the ubiquitin–proteasome and the autophagy–lysosomal systems, increased oxidative stress, mitochondrial dysfunction, inflammation, and other pathogenic mechanisms.^{4,5}

Clinical Presentation: TRAP

The TRAP acronym describes PD's 4 most salient features:

- Tremor at rest
- Rigidity
- Akinesia (or bradykinesia)
- Postural instability

Nonmotor symptoms are common and underappreciated.⁶ These include autonomic dysfunction (orthostatic hypotension, sweating, and sphincter dysfunction), cognitive/neurobehavioral disorders, and sensory and sleep abnormalities.⁷

Rest tremor, easily recognized, is unilateral, occurs at frequencies between 4 and 6 Hz, is almost always prominent in distal extremities, and disappears with action and during sleep. Supination–pronation ("pill-rolling") tremors spread from one hand to the other. Rest tremor can also involve the lips, chin, jaw, and legs. The neck, head, or voice are usually uninvolved.⁸ Among patients, tremor patterns vary and change over time.⁹

Rigidity is increased resistance, usually demonstrated by the "cogwheel" phenomenon—circular jerking rigidity in flexion and extension in a background of tremor, which continues throughout an entire range of movement.¹⁰ It can be painful, and painful shoulder is one of PD's most frequent initial manifestations.^{11,12} Rigidity of the neck and trunk may cause postural deformities, generally late in the disease.¹³ One of PD's most disabling symptoms, acute immobility episodes (or freezing), may make patients unable to rise from a chair, speak, or walk; although these often occur toward the end of the dose interval, they can be spontaneous and unpredictable.¹⁴

Bradykinesia, or slow movement, is PD's most characteristic clinical feature. Initially, it creates difficulty with ordinary activities and slow movement and reaction times.^{15,16} It progresses to difficulty in planning, initiating, and executing movement; patients also have trouble performing sequential and simultaneous tasks.¹⁷ Fine motor tasks (eg, buttoning, holding a pen or eating utensils) suffer. Eventually, patients become "frozen" and cannot gesture, drool because of impaired swallowing,¹⁸ lose facial expression, and walk rigidly. Paradoxically, patients who become excited or alarmed may be able to move quickly to catch a ball (or may run if someone screams "fire"). Bradykinesia appears to be related to degree of dopamine deficiency.¹⁹

Postural instability occurs as the patient loses postural reflexes, often at the late stages of PD. Postural instability frequently causes falls, many of which lead to hip fractures.²⁰

Treating Parkinson's: Medication

The Table describes drugs used in PD. Clinicians work with individuals and consider each drug's relative efficacy and adverse effect profile; the patient's comorbidity, employment status, and preference; and experience. For obvious reasons, drug treatment usually begins with dopamine replacement therapy. Levodopa (L-dopa), dopamine's metabolic precursor, prescribed with a peripheral decarboxylase inhibitor to reduce the incidence of nausea and vomiting, generally provides the best symptomatic relief with the fewest short-term adverse effects.²¹

For resistant tremor, clinicians may use anticholinergic drugs as an L-dopa alternative, but they are usually ineffective for other parkinsonism features.²¹

The dopamine agonists or the monoamine oxidase B (MAO-B) inhibitors can be used early as monotherapy to improve symptoms. They block dopamine breakdown and extend L-dopa dose's duration of action. In patients unresponsive to L-dopa, or in those who are not responding as well as they had been, dopamine agonists as adjunct therapy can allow an L-dopa dose reduction. Selegiline's

metabolites— amphetamine and methamphetamine— may inhibit dopamine reuptake and enhance dopamine release. Rasagiline is a second-generation MAO-B inhibitor. Unlike selegiline, it lacks amphetamine metabolites.^{21,22}

Catechol-O-methyl transferase inhibitors increase the peripheral half-life of levodopa, thereby delivering more levodopa to the brain over a longer period of time.^{21,22}

Implications for Pharmacists

Because of PD's slow and chronic course, pharmacists will see these patients or their caregivers frequently. Pharmacists need to be particularly vigilant about medication interactions and ensure dosing changes are gradual rather than abrupt. They should also ask often about swallowing difficulties and offer alternatives when patients begin to have difficulty with oral medications. Advising patients to always ask before crushing oral dosage forms from new prescriptions should be an every-visit reminder. Also, pharmacists must anticipate that childproof closures and blister packs will present challenges for the PD patient, and take appropriate action proactively. ■

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