INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Treatment of Parkinson's Disease***
-April 2025-

Background:
The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) undertook an updated drug class review of medications used to manage the motor symptoms of Parkinson's disease, last reviewed in 2019. The IHS National Core Formulary (NCF) currently includes immediate release (IR) formulations of carbidopa/levodopa and pramipexole. On the basis of the current review, **no modifications** were made to the NCF.

Discussion:
Parkinson's disease is a progressive neurodegenerative disorder characterized primarily by its motor symptoms, including slowing of movement (bradykinesia) accompanied by tremor, muscle rigidity, and painful muscle cramping (dystonia). It affects 1% of persons over 60 in the United States (U.S.), impairing ambulation, social interaction, and activities of daily living. Often associated with depression and REM sleep behavior disorders, in later stages it can progress to include autonomic dysfunction (orthostatic hypotension, constipation, bladder dystonia), dementia, and psychosis. Most cases are recognized after age 60, but 5-10% of patients are diagnosed before age 50.[1]

Age-adjusted incidence in studies of North American and European populations is approximately 21/100,000, however a 2012 study of IHS beneficiaries found a 30% higher overall incidence of 29/100,000.[2,3] Risk associations include exposure to industrial lubricants, agricultural pesticides and farm work, family history, and type 2 diabetes. The pathophysiologic basis for the disease is excessive apoptosis of dopaminergic neurons in the brain's basal ganglia, particularly the substantia nigra, from which more than ½ of such cells have disappeared by the time the diagnosis is made.[4] Hence, most available medicines improve motor function by increasing CNS dopamine levels. To date, no treatment has been shown to slow or alter the natural course of Parkinson's disease.

Carbidopa/ Levodopa
Approved by the U.S. Food and Drug Administration (FDA) in 1975, the dopamine precursor levodopa (LD) is combined in an oral formulation with the dopamine decarboxylase inhibitor carbidopa, slowing peripheral breakdown of LD prior to its crossing the blood-brain barrier, allowing for use of lower doses and reduced nausea. The IR formulation is preferred early in treatment due to its more predictable absorption.[5] LD improves quality of life and motor function more effectively than other dopaminergic agents early in the course of treatment, but after 5 years about half of patients develop motor fluctuations and dyskinesia (involuntary choreiform movements) which require dose adjustments and use of adjunctive agents.[6, 7] Historically, this has been seen as a reason to delay or use alternatives to LD in early treatment.[8] However, several studies comparing early to delayed initiation of LD have shown no difference in length of life or in the long-term rate of developing motor fluctuations and dyskinesia. Quality-of-life scores in patients using levodopa early after diagnosis have been shown to be the same or better compared with those randomized to alternative initial agents.[9-11] The advent of motor fluctuations associated with LD use are now seen as primarily functions of disease progression, rather than being "caused" by LD.[8]

Non-ergot dopamine agonists
Cabergoline and bromocriptine are ergot-derived dopamine receptor agonists (DRAs) which are rarely used for PD management in the U.S. due to their association with cardiac valve, pulmonary and retroperitoneal fibrosis. In their place, the non-ergot DRAs, ropinirole and pramipexole – both available in IR and delayed-release formulations – and rotigotine, available as a transdermal patch, have been developed for use both as initial treatment and as adjuncts in the management of levodopa-associated motor fluctuations. The 2021 American Academy of Neurology practice guideline on the use of dopaminergic therapy for motor symptoms allows for early DRA use in patients with mild motor symptoms as an alternative to levodopa, particularly for younger, thinner, and female patients – characteristics associated with a greater risk of dyskinesia.[6, 7] DRAs should be avoided in those with a history of impulse-control behavioral disorders and older patients in whom adverse effects such as hallucinations, cognitive impairment, and daytime sleepiness can be more problematic.[5] A 2021 meta-analysis suggested that among DRAs, oral pramipexole is second only to injected apomorphine in effectiveness for management of levodopa-associated motor fluctuations.[12]

Monoamine oxidase B inhibitors (MAO-BI)
Inhibition of the enzyme monoamine oxidase B, which degrades dopamine in the CNS, has been shown to improve motor symptoms of PD. These agents (e.g., selegiline, rasagiline) can be used as early, once-daily monotherapy for mild symptoms or added to levodopa as an adjunct for motor fluctuations and dyskinesia. A 2020 multiple treatment comparison meta-analysis showed selegiline to have a relatively greater effect size relative to other DRAs and MAO-BIs

compared to placebo with levodopa (the DRA pramipexole was shown to be the next most effective).[13] A separate open label 2022 trial comparing adjunctive agents showed that DRAs and MAO-BIs outperformed catechol-O-methyltransferase inhibitors in measures of mobility and quality of life over a 4.5-year period.[14] Some evidence has suggested that MAO B-Is may have a neuro-protective effect but their use for this purpose is not recommended pending more robust evidence to support this.[15] Adverse effects include headache and nausea, with hallucinations an impulse control disorders occurring rarely.

Catechol-O-methyltransferase inhibitors (COMTI)

COMTIs (e.g., entacapone, tolcapone, opicapone) are also dopaminergic in the sense that this class of drugs inhibits degradation of levodopa. They are used exclusively as LD add-on therapy to increase "on" time and manage dyskinesia. Though the 2017 NICE guideline suggests they may be offered as an alternative to DRAs and MAOBIs in this setting, their expense may limit use. Use of tolcapone, though appearing to be the most effective of this group, is limited by its association with fulminant hepatic failure.[16]

Other (non-dopaminergic) oral agents

The anticholinergics trihexyphenidyl and benztropine have been used historically for management of tremor-predominant motor symptoms in early PD, but their use as adjunctive treatment is discouraged due to their association with cognitive decline in older patients.[15] Amantadine has been used for more than 50 years for motor symptoms of PD. A long-acting formulation was approved by the FDA in 2017 specifically to treat dyskinesia. According to the 2019 Canadian guideline for Parkinson Disease, there is insufficient evidence to support its use as early treatment, but amantadine is recommended as adjunctive treatment for dyskinesia.[17] Edema and livedo reticularis are associated adverse effects. Istradefylline, approved in 2019 is a novel adenosine A2A antagonist used as add-on therapy to levodopa. Evidence from multiple randomized controlled trials and 2 follow-up open label trials shows it reduces daily "off" time by about 45 minutes.[18]

Findings:

Levodopa may safely be used early for the management of significant motor symptoms for most patients, as the inevitable advent of treatment-related motor fluctuations and dyskinesia are likely a function of disease progression which is associated with but not caused by this treatment. The DRAs and MAOIs, likely more than COMTIs, can be effective adjuncts to levodopa to reduce "off" time and improve good quality "on" time (i.e., with less troublesome dyskinesia). Newer subcutaneous dopaminergic infusion therapies may improve motor fluctuations for patients whose symptoms are difficult to manage with oral levodopa formulations or adjuncts. Where motor symptoms and dyskinesia are poorly controlled with medicines, neurosurgical deep brain stimulation is probably helpful but studies are prone to bias.[19]

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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