Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Parkinson's Disease***
-July 2019-

Background:
In July 2019, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed symptomatic treatments for Parkinson's disease. Following evaluation of clinical, pharmacoeconomic, utilization and pharmacoepidemiologic data, the NPTC voted to **ADD immediate-release carbidopa/levodopa to the IHS National Core Formulary.**

Discussion:
Parkinson's disease can affect almost every body system, in addition to causing bradykinesia plus either tremor, rigidity or both- a clinical syndrome more commonly known as Parkinsonism. Parkinson's disease must be distinguished from other causes of primary degenerative Parkinsonism, and from secondary (iatrogenic) causes such as typical antipsychotics, calcium channel blockers, and antiepileptic drugs. Parkinson's disease is now known to affect not only dopaminergic neurons, but also cholinergic, norepinephrinergic, and serotonergic neurons in widespread areas of the brain. Nevertheless, current therapies including recently approved medications continue to focus on the dopaminergic pathway. The classic therapy, carbidopa/levodopa (CD/LD), remains widely recognized as the most effective therapy for motor symptoms. Combination CD/LD results in the greatest overall improvement in Parkinson's symptoms and quality of life[1-4].

Pharmacotherapeutic Options for <u>early/mild</u> Parkinson's:
<u>CD/LD:</u> While universally agreed to be the most effective treatment, CD/LD has two major limitations: frequent dosing and motor complications. The frequency of CD/LD administration ranges from 3 to 5 times daily for most patients. Furthermore, motor complications may include both dyskinesias (dystonia, chorea, ballism) and an unpredictable response to medication. As Parkinson's disease progresses, maintaining treatment within the therapeutic window becomes more difficult. Despite consistent dosing, response to medication varies and may either erratically fail to reach the therapeutic window, exceed it, or prematurely fall below it. Data from routine CD/LD use in patients demonstrates that approximately 20% of Parkinson's disease patients will experience motor complications after 5 years[5].

<u>Dopamine Agonists (DAs):</u> Both ropinirole and pramipexole offer once-daily formulations. Rivastigmine is also available but is expensive and was determined to confer no advantages beyond transdermal administration. While DAs reduce motor complications comparatively to CD/LD, they lack any appreciable improvement in overall control of Parkinson's disease or quality of life. Dopamine agonists have high rates of adverse drug reactions including devastating psychiatric effects (e.g., hallucinations, impulse control disorders, and dopamine dysregulation syndrome)[6-8]. These adverse reactions are far more common in patients aged 65 years and older, which includes most Parkinson's patients[9].

<u>Monoamine Oxidase "B" inhibitors (MAOIs):</u> Both selegiline and rasagiline have once-daily formulations as well. Safinamide is also available but is more expensive and confers no advantages beyond novelty. While MAOIs reduce the incidence of motor complications (vs. CD/LD), much like the DAs, they also do not improve overall control of Parkinson's or improve patient's quality of life[6]. While less problematic than non-selective MAOIs, the irreversible selective MAOIs still have a large number of category D and X drug-drug interactions with other commonly used medications. Patients on MAOIs must also limit intake of a long list of tyramine-rich foods[9].

No available therapeutic strategy modifies the course of Parkinson's disease. In particular, recent evidence provides reassurance that early use of CD/LD does not hasten the onset of motor complications[10]. European and Canadian guidelines suggest using any of the above medications for early Parkinson's[2,3]. The NICE guidelines recommend CD/LD for motor symptoms that impact quality of life[1].

Pharmacotherapeutic Options for <u>advanced</u> Parkinson's:
All patients with advanced Parkinson's disease require the administration of CD/LD for symptomatic control although clinicians may consider longer-acting formulations or adjuvant pharmacologic treatments:

Controlled-release CD/LD: Across studies, benefits have been inconsistent and mostly minor in terms of patient impact. Furthermore, due to inconsistent gut absorption, it is difficult for patients to predict when they will receive a therapeutic response[2].

Extended-release CD/LD: Extended-release CD/LD is simply a combination of immediate-release and controlled-release formulations of CD/LD, thereby theoretically providing a more predictable onset of therapeutic response with a consistent and prolonged duration of action. One Phase 3 study in particular directly compared the efficacy of extended-release CD/LD with immediate-release CD/LD. Despite questionable identification and reporting of the study's primary and secondary endpoints after completion of the trial (as documented in ClinicalTrials.gov), the highly-conflicted study investigators were unable to prove a clinically significant overall improvement in Parkinson's symptoms[11]. Furthermore, extended-release CD/LD still requires frequent dosing of at least 3 times daily and does not reduce pill burden.

The Cochrane Database and the National Institute for Health and Care Excellence (NICE) guidelines provide the most detailed and rigorous comparison of adjuvant treatments[1,12]:

Dopamine Agonists: Provide the greatest reduction in motor symptoms and overall improvement, but with the highest rate of dyskinesias and the psychiatric side effects discussed above.
MAOIs: Effective, with a lower rate of side effects, but with the extensive food and drug interactions discussed above.
Catechol-O-methyltransferase Inhibitors: Effective, but with the highest rate of side effects.
Amantadine: No acceptable evidence of benefit.

Findings:

In patients with early Parkinson's disease and mild symptoms, DAs may be considered for younger patients while MAOIs can be used for patients on few medications who are able to manage potential food and drug interactions. However, these indications were not considered compelling or common enough to require inclusion of these alternatives on the IHS National Core Formulary. DAs are also often used for other indications (e.g., restless leg syndrome) but these are outside the scope of this review.

Despite some limitations, CD/LD remains the best option for management of the symptoms of Parkinson's disease, across the spectrum of severity.

While most patients with advanced Parkinson's disease benefit from adjuvant therapy, neither the currently-available medical evidence nor internal pharmacoeconomic review justify selection of any adjuvant products to the National Core Formulary.

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.

References:

1. National Institute of Health and Care Excellence. Parkinson's disease in adults. NICE guidelines: July 2017.
2. Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. *Eur J Neurol*. 2013; 20(1):5–15.
3. Grimes D, Gordon J, Snelgrove B, et al. Canadian Guidelines on Parkinson's Disease. *J Can Sci Neurol.* 2012; 39(4 Suppl 4):S1-30.
4. Connolly BS, Lang AE. Pharmacological Treatment of Parkinson Disease: A Review. *JAMA.* 2014; 311(16):1670–83.
5. Block G, Liss C, Reines S, et al. Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease. *Eur Neurol Basel*. 1997; 37(1):23.
6. PD MED Collaborative Group. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet*. 2014; 384(9949):1196–205.
7. Holloway R, Marek K, Biglan K, et al. Long-term Effect of Initiating Pramipexole vs Levodopa in Early Parkinson Disease. *Arch Neurol.* 2009; 66(5):563–70.
8. Hauser RA, Rascol O, Korczyn AD, et al. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. *Mov Disord.* 2007; 22(16):2409–17.
9. Pharmacologic treatment of Parkinson disease - UpToDate [Internet]. [cited 1/13/19].
10. Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. *N Engl J* Med. 2019; 380(4):315–24.
11. Hauser RA, Hsu A, Kell S, et al. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. *Lancet Neurol.* 2013; 12(4):346–56.
12. Stowe R, Ives N, Clarke CE, et al. Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson´s disease patients with motor complications. *Cochrane Database Syst Rev* [Internet]. 2010 [cited 1/19/19].