Addressing Nonmotor Symptoms May Improve On-Off Management in Parkinson's Disease

Symptomatic patients with Parkinson's disease (PD) usually respond well for several years to the "gold standard" of treatment, levodopa with carbidopa, but eventually and almost invariably, the patient begins to experience "wearing-off" or, the "on-off" phenomenon.[1,2] "On" is the term used to describe an individual's experience of the full effect of levodopa (or other dopaminergic medication) and "off" describes the breakthrough of motor and nonmotor PD symptoms, before a next dose is due. Although the development of worsening "on-off" tends to parallel the progressive deterioration of the dopamine-producing substantia nigra cells, other factors have been implicated as possible contributing factors.

Gap: As Parkinson's disease (PD) progresses, patients may begin to experience off episodes related to their PD medication. Onset and severity of motor and nonmotor symptoms vary with individuals, negatively impacts quality of life, and is under-recognized.

Learning Objective: Identify causes, risk factors, and consequences of motor and nonmotor symptoms related to the on-off phenomenon in patients with Parkinson's disease.

"Off "occurs when a levodopa dose wears off prior to the next due dose, when it "kicks-in" late, when a dose doesn't work at all, or when a patient wakes up with morning motor symptoms (morning akinesia) because the night dose "wore off." [2] "Off" can occur unpredictably, affecting one's ability to function independently, and affecting quality of life. Breakthrough symptoms that characterize "off" are the hallmark motor symptoms of Parkinson's: bradykinesia, resting tremor, rigidity, and postural instability, as well as any of the other motor and nonmotor symptoms of PD. [2] In the early stages of this erratic on-off phenomenon, a physician may increase the dose and/or frequency of carbidopa /levodopa (CD/LD), but at some point, the dose is limited by the occurrence of dyskinesia, which is a side-effect of high-dose levodopa. When this happens, or even earlier in the diagnosis, the clinician may add adjuvant medications to the mainstay regimen, in the hope of decreasing "off" time, increasing "on" time, and limiting side effects of levodopa. [2]

Recently, experts on PD have pointed out that traditionally there has been a myopic focus on treating motor symptoms of Parkinson's, but patient reports show that nonmotor symptoms (NMS) have greater bearing on quality of life, compared with motor symptoms.[3,4,5,6] In addition, some of the most common nonmotor issues may be implicated in contributing to "on-off", and several therapies have emerged to address some of these complicating issues.

While the motor symptoms of Parkinson's are well known by most neurologists, NMS may be less well recognized, or the associated issues may not be given due consideration by busy physicians. NMS include neuropsychiatric issues such as depression, anxiety and apathy, fatigue, daytime sleepiness, insomnia, and REM sleep disorders; and GI disorders, such as constipation, gastroparesis, and small intestine bacterial overgrowth (SIBO.) Drug adherence can be an issue when there are neuropsychiatric, cognitive, or sleep-related effects of the disease. There is also the issue of drug absorption, with gastroparesis, bacterial overgrowth, and even mistimed protein ingestion, all potentially interfering with levodopa absorption. These factors can lead to an increase in "off" time.[3,4,5,6]

Although there are available adjunct therapies that can be added to the CD/LD regimen, patients often continue to struggle with episodes of "on- off" and episodes of levodopa-induced dyskinesia, posing a balancing act that can be hard for physician, patient, and caregiver to manage.[7] Patients may also not be aware of just how much time is spent in "off". One study that had patients record their time in "off" found that many of the participants were surprised by the results.[8,9] With increasing time spent in "off", a patient is at risk for falls, accidents, and choking. Stigma or embarrassment can also be a consequence, and lead to isolation and loss of independence.

Gap: Patients are often challenged to recognize off symptoms of PD, especially if they are mild. If unreported and treatment is not optimized, off episodes can impact quality of life, gait and stability, and lead to negative consequences.

Learning Objective: Integrate validated tools to determine patterns of motor and nonmotor off episodes to uncover patterns and severity of symptoms.

The Wearing-Off questionnaire (WOQ-19) was used in a study in Europe to assess the effects of various combinations of treatments on patients with PD in varying stages. 73 patients were assessed using the WOQ-19 for motor and nonmotor symptoms; nonmotor symptoms prevailed but there was correlation of nonmotor and motor effects of "off", with two other scales often used to measure motor symptoms of "off". [7] The WOQ- 19 was recently found to be a reliable and validated measure of "off."[9] A questionnaire that can identify nonmotor and motor "off" times can add to the holistic and balanced picture of "on-off" in PD, used as a tool by a patient and doctor for personalizing treatment.

Gap: Even with optimization of treatment, patients still experience off periods, underscoring the need for new therapeutic options.

Learning Objectives: Evaluate clinical efficacy and safety of current and emerging therapies to optimize treatment and minimize off times in patients with PD.

Considering the prevalence of delayed gastric emptying and SIBO in PD patients, it is encouraging that new delivery methods are allowing levodopa and dopamine agonists to be delivered in a way that can stabilize plasma levels, and/or can be used on-demand as "rescue" treatment of "off" episodes. A carbidopa/levodopa gel has been available in the US for several years now and is delivered as a 16-hour infusion directly to the small bowel via a J-tube or extended gastric tube, thereby increasing absorption, and maintaining steady plasma levels of levodopa. And, in late 2018, the FDA approved a carbidopa/levodopa inhaler to be used as a rescue treatment of "off' periods in patients with "off" episodes on CD/LD.[10]

Apomorphine is a dopamine agonist with similar efficacy to levodopa and has been available in Europe as a continuous subcutaneous infusion via pump. It is also available in the US as intermittent subcutaneous injections, which can be used on-demand for "off" episodes. Of course, many patients are needle-averse, and there is also a risk of infection and injection-site reaction, so still other delivery methods are needed. In the US, apomorphine, delivered via sublingual film, performed well in phase 3 trials, and will soon be available, pending FDA approval.[11]

Dopamine agonists exert dopaminergic effect but are less likely than levodopa to cause dyskinesia.[12] Because of this, they are often used as initial monotherapy in young patients diagnosed before age 45. This allows the initiation (and eventual maxing-out) of levodopa dosing to be postponed, hopefully forestalling "on-off." Dopamine agonists can also be useful in patients with "levodopa phobia", which is an artifact of old notions--- perhaps because of past media and industry influence---that levodopa makes PD "worse"; the desire to avoid dyskinesia and "on-off" means that some patients, and even some doctors, have hesitated to use levodopa at all.[13] However, although dopamine agonists have been shown to be less likely than levodopa to cause dyskinesia, they are also less effective at controlling PD symptoms such as "freezing" while walking.[12]

Dopamine agonists can also be added to the carbidopa/levodopa regimen to help bridge the "wearing-off" time. However, dopamine agonists can have side effects, especially in the elderly, including orthostatic hypotension, heart failure, heart valve disease, somnolence, and hallucinations. Several studies have documented an increase in impulse control disorder in patients taking dopamine agonists.[14]

Enzyme inhibitors may be added to CD/LD to help mitigate "on-off." These include monoamine oxidase-B (MAO-B) inhibitors and catechol-O- methyltransferase (COMT) inhibitors. MAO-B inhibitors reduce the breakdown of dopamine in the brain, whereas COMT-inhibitors prevent peripheral metabolism of levodopa to dopamine, leaving more levodopa available to cross the blood-brain barrier, to be converted to dopamine in the brain where it is needed. Safinamide, a new MAO-B inhibitor recently approved by the FDA for the treatment of "off" episodes in patients with PD taking CD/LD, has been shown to increase "on" time without dyskinesia, and to decrease "off" time.[15]

In two large phase 3 trials, opicapone, a COMT-inhibitor, was shown to increase "on" times in people maintained on levodopa or other dopaminergic treatments. This drug was effective at increasing "on" and did not result in the severe diarrhea that can occur with epicapone and tolpicapone. Tolpicapone can also be hepatotoxic, which has not been shown to be the case with opicapone. [16,17] This drug is not yet available in the US but has been on the market in Europe for a few years.

For the treatment of tremors due to PD, anticholinergics, such as benztropine, may be used. Benztropine decreases dopamine reuptake in the brain, and also relaxes smooth muscles, which can therefore facilitate gastric emptying and intestinal absorption of levodopa, but the drug also can have a dampening effect on the dyskinetic effects of levodopa.[18] However, the only drug specifically approved by the FDA to treat dyskinesia in PD patients taking levodopa, is amantadine, which is not an anticholinergic, but actually an antiviral medication.[19,20]

Intractable cases of dyskinesia have sometimes improved with deep brain stimulation, or DBS, and some patients getting DBS are able to decrease their oral medications. Studies are underway, looking at the effects of placing electrodes at various points in the brain, in the hope that DBS can be used to control a greater range of PD symptoms. [21]

Finally, technology continues to be explored and advanced in the attempt to improve on the core problem, which is maintaining steady plasma levels of levodopa. A multi-center, randomized, phase 3 study in Europe, Israel, and the US, is looking at a new technology called an "accordion pill", which is showing signs of being effective in reducing "off" time. As of April 2019, 90% of the patients in this randomized trial have signed up to continue in the open-label extension study. The accordion pill technology involves a CD/LD-infused film folded into a capsule, which remains in the stomach, but slowly releases medication into the upper intestine, for gradual, steady absorption.[22]

Managing Parkinson's disease continues to be a challenge, as the medication that is most effective in treating the symptoms is the same medication that starts to become problematic with long-term use. Patients can be engaged as valuable partners in the quest to develop better treatments and new technologies, to decrease "off" times and side-effects, so that they may find balance in the management of this complex disease.

References

1. Poewe W, Antonini A, Zijlmans JC, Burkhard PR, Vingerhoets F. Levodopa in the treatment of Parkinson's disease: An old drug still going strong. *Clin Interv Aging*. 2010;5:229-238. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938030/. Accessed July 13, 2019.
2. Lees AJ. The on-off phenomenon. *Journal of neurology, neurosurgery, and psychiatry*. 1989;Suppl:29-37. doi:10.1136/jnnp.52.Suppl.29
3. Wu S-L, Liscic RM, Kim S, Sorbi S, Yang Y-H. Nonmotor Symptoms of Parkinson's Disease. *Parkinsons Dis*. 2017;2017. doi:10.1155/2017/4382518
4. Tibar H, El Bayad K, Bouhouche A, et al. Non-Motor Symptoms of Parkinson's Disease and Their Impact on Quality of Life in a Cohort of Moroccan Patients. *Front Neurol*. 2018;9. doi:10.3389/fneur.2018.00170
5. Titova N, Chaudhuri KR. Non-motor Parkinson disease: New concepts and personalised management. *Medical Journal of Australia*. 2018;208(9):404-409. doi:10.5694/mja17.00993
6. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry*. 2000;69(3):308-312. doi:10.1136/jnnp.69.3.308
7. Pistacchi M, Gioulis M, Sanson F, Marsala SZ. Wearing off: A complex phenomenon often poorly recognized in Parkinson's disease. A study with the WOQ-19 questionnaire. *Neurology India*. 2017;65(6):1271. doi:10.4103/0028-3886.217959
8. Stacy M. The wearing-off phenomenon and the use of questionnaires to facilitate its recognition in Parkinson's disease. *J Neural Transm (Vienna)*. 2010;117(7):837-846. doi:10.1007/s00702-010-0424-5
9. Mantese CE, Schumacher-Schuh A, Rieder CRM. Clinimetrics of the 9- and 19-Item Wearing-Off Questionnaire: A Systematic Review. Parkinson's Disease. doi:10.1155/2018/5308491
10. Paul S. FDA Approves Inbrija™ (levodopa inhalation powder) Parkinson's disease. *APDA*. December 2018. https://www.apdaparkinson.org/article/fda-approves- inbrija-off-parkinsons-disease/. Accessed July 15, 2019.
11. Potential Parkinson's Treatment for Off Periods Shows "Key Benefit" of Working Well, Sunovion Says. *Parkinson's News Today*. October 2018. https://parkinsonsnewstoday.com/2018/10/08/sunovion-expects-apl-130277-ably-treats-off-episodes-awaits-fda-decision-interview-story/. Accessed July 15, 2019.
12. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med*. 2000;342(20):1484-1491. doi:10.1056/NEJM200005183422004

13. Titova N, Levin O, Katunina E, Chaudhuri KR. 'Levodopa Phobia': A review of a not uncommon and consequential phenomenon. *Npj Parkinson's Disease*. 2018;4(1):31. doi:10.1038/s41531-018-0067-z

14. Borovac JA. Side effects of a dopamine agonist therapy for Parkinson's disease: A mini-review of clinical pharmacology. *Yale J Biol Med*. 2016;89(1):37-47. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4797835/. Accessed July 15, 2019.

15. Fala L. Xadago (Safinamide), an Oral MAO-B Inhibitor, FDA Approved as Adjunctive Treatment for Patients with Parkinson's Disease. April 2018. http://www.ahdbonline.com/issues/2018/april-2018-vol-11-ninth-annual-payers-guide/2551-xadago-safinamide-an-oral-mao-b-inhibitor-fda-approved-as- adjunctive-treatment-for-patients-with-parkinson-s-disease. Accessed July 15, 2019.

16. Waters C. Practical issues with COMT inhibitors in Parkinson's disease. *Neurology*. 2000;55(11 Suppl 4):S57-59; discussion S60-64.

17. Kaakkola S. Problems with the present inhibitors and a relevance of new and improved COMT inhibitors in Parkinson's disease. *Int Rev Neurobiol*. 2010;95:207-
225. doi:10.1016/B978-0-12-381326-8.00009-0

18. Cogentin (Benztropine). *Parkinson's News Today*. https://parkinsonsnewstoday.com/parkinsons-disease-treatments/motor-symptoms/cogentin-benztropine/. Accessed July 15, 2019.

19. Pahwa R, Tanner CM, Hauser RA, et al. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study): A Randomized Clinical Trial. *JAMA Neurol*. 2017;74(8):941-949. doi:10.1001/jamaneurol.2017.0943

20. FDA Approves Amantadine Hydrochloride for Dyskinesia. MD Magazine. https://www.mdmag.com/medical-news/fda-approves-amantadine-hydrochloride-for- levodopainduced-dyskinesia. Accessed July 15, 2019.

21. Deep Brain Stimulation. The Michael J. Fox Foundation for Parkinson's Research | Parkinson's Disease. https://www.michaeljfox.org/news/deep-brain- stimulation. Accessed July 15, 2019.

22. Intec Pharma Reports Last Patient Last Visit in Pivotal Phase 3 Trial of Accordion Pill™ Carbidopa/Levodopa for the Treatment of Advanced Parkinson's Disease Patients. BioSpace. https://www.biospace.com/article/intec-pharma-reports-last-patient-last-visit-in-pivotal-phase-3-trial-of-accordion-pill-carbidopa- levodopa-for-the-treatment-of-advanced-parkinson-s-disease-patients/. Accessed July 15, 2019.