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Focus on Symptom Fluctuations in Parkinson's Disease

By Richard Kilmartin

Parkinson's disease (PD) is a progressive, neurodegenerative disease with debilitating motor symptoms including tremor, stiffness, and a slowing of movements called bradykinesia. PD often includes underrecognized non-motor symptoms such as pain, constipation, urinary incontinence, cognitive impairment, and changes in mood (e.g., anxiety, depression). These motor and non-motor symptoms can become increasingly bothersome over time and first-line medications for PD, such as levodopa, may no longer control symptoms at previously effective doses. Individuals may experience fluctuations between good symptom control called "**on**" times and worsening symptoms or "**off**" times. These fluctuations may also be referred to as wearing off, motor fluctuation, or "on-off" and can limit one's ability to participate in self-care and daily activities. Symptom fluctuations can vary in frequency and intensity. For some, they are predictable, where symptoms increase between medication doses or at a particular time of day (e.g., early morning stiffness). For others, "off" episodes can be unpredictable and quite severe, including a temporary but highly debilitating condition referred to as "freezing" where individuals experience a nearly complete inability to move parts of their body.

Strategies to improve function and quality of life, by reducing the severity and duration of fluctuations between "on" and "off", are generally broken into three approaches: 1) adjusting levodopa therapy, 2) the addition of another medication or adjunct, and 3) the use of as needed medications for rapid symptom relief. When selecting the best strategy, it is important to use a person-centered approach and consider drug interactions, available dosage forms, and potential adverse effects. For example, medication-induced vomiting or sudden involuntary movements could limit an individual's willingness to adhere to treatment. Likewise, someone experiencing motor fluctuations involving the upper limbs or face may find certain products (e.g., injection, inhaler) difficult to use. Additional considerations are listed in the tables below but are not all-inclusive of the options available. Consultation with a specialist, where appropriate, should be considered.

Adjusting the levodopa dose or timing	
Levodopa is a cornerstone in PD treatment, and while dosage increases may be necessary, this strategy becomes less reliable as PD progresses.	
Diet modifications	Avoiding protein-rich foods within 60 minutes of levodopa administration may help improve absorption
Dosing interval adjustment	Administering lower doses more frequently (e.g., every 4 hours vs. every 6 hours) may improve symptoms while avoiding involuntary movements or peak dyskinesia
Longer-acting levodopa products • carbidopa/levodopa CR (e.g., Sinemet CR) • carbidopa/levodopa ER (e.g., Rytary)	Longer acting products smooth the rise and fall of drug concentrations, improving symptom control • Better evidence for the effectiveness of the ER product over the CR product for management of "off" episodes • The CR product may be helpful with nighttime or early morning symptoms

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Adding an adjunct medication to reduce "off" time	
Adjunctive therapy may be beneficial when levodopa adjustments are no longer effective or tolerated.	
Dopamine agonists • Pramipexole (Mirapex, Mirapex ER) • Ropinirole (Requip, Requip XL) • Rotigotine patch (Neupro)	• Hallucinations, impulse control, or hypotension may limit tolerability, especially in older adults with cognitive impairment • Avoid rotigotine in those with sulfite allergy
Catechol-O-methyl transferase (COMT) inhibitors • Entacapone (Comtan, Stalevo) • Opicapone (Ongentys) • Tolcapone (Tasmar)	• Entacapone is administered at the same time as levodopa/carbidopa and is available alone or as a fixed dose combination • Opicapone should be administered at bedtime 1 hour before or after food • Tolcapone has a BOXED WARNING describing an increased risk of severe liver injury
Monoamine oxidase (MAO) type B inhibitors • Rasagiline (Azilect) • Safinamide (Xadago) • Selegiline (Zelapar)	• May require dietary restriction (i.e., tyramine-containing foods) to avoid severe hypertension • Avoid use with interacting medications (e.g., tramadol, methadone, some antidepressants, other MAO inhibitors) • Selegiline is available as an orally disintegrating tablet that is administered in the morning, without food or drink
Adenosine A2A receptor antagonists • Istradefylline (Nourianz)	• Drug interactions may require dose reduction (e.g., azole antifungals) or complete avoidance (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) • Monitor closely for involuntary movements, dizziness, or hallucinations

Adding as needed medication for rapid relief of "off" episodes	
As needed or rescue therapies can be used to address the wearing off or delayed "on" that can occur between levodopa doses and may be especially beneficial for unpredictable "off" episodes.	
• Apomorphine injection (Apokyn) • Apomorphine sublingual film (Kynmobi)	• Requires initial administrations under supervision • Severe nausea and vomiting are common and may require premedication with an antiemetic. Certain antiemetics (e.g., ondansetron) are contraindicated.
Inhaled levodopa (Inbrija)	• Requires dexterity and breathing technique to use the inhalation device
Levodopa/carbidopa intestinal gel (Duopa)	• Delivered directly into the small intestine over 16 hours • Requires the insertion of a feeding tube

Subtle non-motor symptoms related to PD may be mistaken for other conditions. Mood changes, incontinence, and increased falls should prompt reevaluation of the medication regimen and underlying cause.

Awareness of the therapeutic options for PD symptom fluctuations and close monitoring to identify bothersome symptoms or adverse medication effects can significantly improve the quality of life for older adults with PD.

Common Concepts About Medical Foods

by Carrie Allen

Products called medical foods (e.g., Vasculera, CerefolinNAC, Axona, Limbrel, Deplin) are becoming more common, and are often confused with prescription drugs or prescription dietary products. As they do not fit into either category, they are different in terms of reimbursement and regulatory oversight. A brief summary of questions and answers published by the FDA on medical foods is below.

What are medical foods?
Medical foods are not those simply recommended by a physician as part of an overall diet to manage the symptoms or reduce the risk of a disease or condition. They are foods that are specially formulated and processed (as opposed to a naturally occurring food) for a patient who requires use of the product as a major component of a disease or condition's specific dietary management.

Does FDA regulate medical foods as drugs or require that medical foods be made available by written or oral prescription?
No. Medical foods are not drugs; therefore, they are not subject to any regulatory requirements that specifically apply to drugs. The federal requirements for a written or oral prescription only applies to the dispensing of prescription drug products. Medical foods must conform only to those regulations dealing with general food safety and labeling to be distributed in the United States. And they must be formulated to be consumed or administered enterally under the supervision of a physician, but there is no federal requirement for a prescription.

How does FDA interpret "under the supervision of a physician"?
FDA considers this to mean that the intended use of a medical food is for the dietary management of a patient receiving active and ongoing medical supervision (e.g., in a health care facility or as an outpatient) by a physician who has determined that the medical food is necessary to the patient's overall medical care. The patient should generally see the physician on a recurring basis for instructions on the use of the medical food as part of the dietary management of a given disease or condition.

Does the FDA maintain a list of medical foods or have a compliance program for medical foods?
Because the FDA does not regulate medical foods, they do not maintain a comprehensive list. They do have a compliance program, which gives direction to FDA inspectors on obtaining information from manufacturers on manufacturing and quality control processes, collecting samples to analyze, and recommending actions when violations of the Food, Drug, and Cosmetic Act occur.

May the labeling of a medical food bear the symbol "Rx only"?
The labeling of medical foods may not bear the symbol "Rx only." However, many medical food websites claim that their products are "prescription products", which can be confusing. Unlike prescription drugs, medical foods are not required by federal law to be dispensed by prescription. Therefore, the use of the symbol "Rx only" in the labeling of a medical food is a false and misleading statement about that product. However, because medical foods are required by statute to be used under the supervision of a physician, the FDA does not object to language to communicate this requirement in the labeling of a medical food product (e.g., "must be used under the supervision of a physician"). When medical foods (or any applicable product) do not follow appropriate labeling requirements or violate manufacturing processes, they are sent a warning letter by the FDA. Those warnings can be found by searching the following website: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters

New Generic Medications

By Allen Lefkovitz

Generic Name	Brand Name	Date Generic Available
Formoterol 20 mcg/2 mL Inhalation Solution	Perforomist® Inhalation Solution	6/25/21
Etravirine 100 mg and 200 mg Tablet	Intelence® Tablet	6/18/21
Lopinavir/Ritonavir 100 mg/25 mg and 200 mg/50 mg Tablet	Kaletra® Tablet	6/11/21
Rufinamide 200 mg and 400 mg Tablet	Banzel® Tablet	6/4/21
Arformoterol 15 mcg/2 mL Inhalation Solution	Brovana® Inhalation Solution	6/4/21
Bepotastine 1.5% Ophthalmic Solution	Bepreve Ophthalmic Solution	6/1/21
Calcitonin Salmon 400 units/2 mL Injection	Miacalcin® Injection	6/1/21
Tiopronin 100 mg Tablet	Thiola® Tablet	5/24/21

New Drug

By Dave Pregizer

Aduhelm™ Injection

Brand Name (Generic Name)	Aduhelm™ [AD-yew-helm] (aducanumab-avwa) [A-due-KAN-ue-mab]
How Supplied	170 mg/1.7 mL (100 mg/mL) solution in a single-dose vial 300 mg/3 mL (100 mg/mL) solution in a single-dose vial
Therapeutic Class	Amyloid beta-directed antibody
Approved Indication	Treatment of Alzheimer's disease. Treatment should be initiated in individuals with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.
Usual Dosing	Titration is required for treatment initiation. Recommended maintenance dose: 10mg/kg in 100 mL of 0.9% sodium chloride as an intravenous infusion over approximately 1 hour every 4 weeks.
Select Drug Interactions	There are no known significant drug interactions
Most Common Side Effects	Headache, falls, amyloid-related imaging abnormalities related to edema (ARIA-E) or hemosiderin deposition (ARIA-H, which can include microhemorrhages or areas of superficial siderosis)
Miscellaneous	• Obtain a brain MRI (within one year) before initiating treatment and prior to the 7th and 12th infusions. • Approved under accelerated approval. Continued approval for the indication may be contingent upon verification of clinical benefit in confirmatory trial(s).
Website	http://www.Aduhelm.com