Poster #123

USE OF ON-DEMAND TREATMENTS FOR OFF EPISODES IN PARKINSON'S DISEASE: GUIDANCE FROM A RAND/UCLA MODIFIED DELPHI CONSENSUS PANEL

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BACKGROUND

- Parkinson's disease (PD) patients on levodopa develop motor fluctuations and often experience OFF episodes with re-emerging parkinsonian symptoms throughout the day despite regular medication use.
- On-demand treatments are designed to provide rapid onset of effect to treat OFF episodes and improve symptoms. However, there is little guidance on how best to use these treatments.

OBJECTIVE

Develop consensus on the use of on-demand treatments (levodopa inhalation powder, apomorphine sublingual film, apomorphine subcutaneous injection) for OFF episodes in patients with Parkinson's disease.

METHODS

We conducted an expert RAND/UCLA Delphi panel (Figure 1).

1. We convened an international panel of experts (11 clinicians, 1 patient advocate) and reviewed evidence on the use of on-demand treatments for OFF episodes. Eight panelists were from the United States (US) and 4 were from outside the US.
2. We collaboratively developed a rating form consisting of 432 unique patient scenarios that varied based on 6 key characteristics (Table 1).
3. Before and after a virtual meeting, panelists rated the appropriateness of prescribing on-demand treatments.
4. At the meeting, panelists discussed areas of disagreement.

After the meeting, consensus statements summarizing the group opinion were drafted.

Figure 1. The RAND/UCLA Delphi Panel Process

Table 1. Clinical Characteristics used to inform patient scenarios

Clinical characteristic	Categories and definitions
Patient's perspective on the functional impact of OFF episodes	• Not interfering with daily activities, but may impact life in other ways[1] • Interfering with some instrumental daily activities[2] • Disabling/interfering with most basic daily activities[3]
Levodopa dose	• Low: total daily dose <400mg or ≤3/day • Medium: total daily dose 400-600mg or 4-5/day • High: total daily dose >600mg or ≥6/day
Adjunctive therapies (i.e., ON-extenders)	• No adjunctive therapies • A dopamine-receptor agonist and possibly other adjunctive therapies • Any other adjunctive therapies excluding dopamine-receptor agonists
Experiencing therapy-related side effects[4]	• No • Yes, including very likely to experience side effects if dose were increased
Frequency or duration of OFF episodes	• Frequent/long duration: ≥2 times/week for early morning OFF, ≥3 times/day or >25% of waking day for other types of OFF • Less frequent/shorter duration: ≤1 time/week for early morning OFF, ≤2 times/day or ≤25% of waking day for other types of OFF
Type of OFF episodes	• Wearing OFF (i.e., the reemergence of parkinsonian symptoms as the effect of levodopa diminishes near the end of the dose interval) • Early morning OFF (i.e., morning slowness or immobility experienced prior to the first medication dose of the day, may also include nocturnal OFF) • Delayed ON (i.e., failure to turn "ON" following a dose of levodopa, resulting in a delayed "ON," dose failure, or "no-ON" response) • >1 type/not described by other categories[5]

[1] Although patient's daily activities are not affected, the OFF episodes do impact their lives in other ways (e.g., fear/reluctance to leave home, decreased job performance).
[2] For example, driving, shopping, cooking, traveling, remembering to take medication, managing finances.
[3] For example, hygiene, self-care, feeding, safety.
[4] Side effects may include an intolerance to levodopa (e.g., nausea, sleepiness/fatigue, symptomatic low blood pressure), other dopaminergic side effects (e.g., troublesome dyskinesia, paranoia, hallucinations), and/or dopaminergic dysregulation syndrome or impulse control disorders (as defined by the DSM-5 [https://dsm.psychiatryonline.org/doi/10.1176/appi.books.9780890425596.dsm15]) that have a marked impact on the patient and cannot be monitored.
[5] This may include unpredictable or unexpected OFF.

RESULTS

- Overall, experts agreed 230 (53%) scenarios were appropriate and 21 (5%) were inappropriate settings to prescribe on-demand treatments. Experts disagreed on 140 (32%) and were uncertain of 41 (9%) of scenarios.
- The panel endorsed the use of on-demand treatment for OFF episodes in the scenarios listed in Table 2.
- Among panelists from the US, the group agreed 62% of scenarios were appropriate settings to prescribe on-demand treatment.

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Table 2. Expert recommendations on when it is appropriate to prescribe on-demand treatments for OFF episodes

Functional impact of OFF episodes on daily activities	Expert recommendation on appropriateness of prescribing on-demand treatments for the patient to take as needed
OFF episodes are disabling and interfere with most basic daily activities	Appropriate in most circumstances.
OFF episodes interfere with some instrumental daily activities	Appropriate if the patient also experiences **any** of the following: • Early morning OFF episodes or >1 type of OFF episode (regardless of frequency). • Frequent/long duration delayed ON episodes, except if the patient is on low/medium dose levodopa without any other adjunctive therapies (i.e., ON-extenders). • Frequent/long duration wearing OFF episodes, except if the patient is on levodopa without any other adjunctive therapies. • Less frequent/shorter wearing OFF episodes and are on high dose levodopa with an adjunctive treatment.
OFF episodes do not interfere with daily activities but can impact patient in other ways	Appropriate if the patient also meets **all** of the following: • Frequent early morning OFF, delayed ON, or >1 type of OFF episode • On high dose levodopa and other adjunctive treatment (other than a dopamine-receptor agonist). • Therapy-related side effects.

CONCLUSIONS

- Panelists agreed on-demand treatment is appropriate for many PD patients with OFF episodes.
- The greater the functional impact of OFF episodes, the more likely panelists were in agreement that on-demand treatment is appropriate to prescribe.
- In a few circumstances, panelists rated on-demand treatment as inappropriate; generally, these were in patients who experienced predictable wearing OFF episodes that had minimal functional impact and were on low or medium dose levodopa without adjunctive therapies.
- In the US, three on-demand treatments are available; internationally, only one on-demand treatment (apomorphine subcutaneous injection) is commercially available. Although agreement was higher when considering only US-panelists, the pattern of agreement (i.e., more agreement with greater functional impact) remained the same compared to the entire panel.
- These recommendations may serve as one of the first guidelines to support clinicians in the appropriate use of on-demand treatments in patients with PD.

- **Limitations**
  - Although all panelists had significant experience in the field and were drawn from a diversity of backgrounds and geographic regions, 12 experts cannot represent the full experience of clinicians who work in this field. Different groups of experts may have reached different conclusions.
  - These results do not identify the scenarios in which each individual on-demand treatment (levodopa inhalation powder, apomorphine sublingual film, apomorphine subcutaneous injection) would be most appropriate.