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Review article

The spectrum of "off" in Parkinson's disease: What have we learned over 40 years?

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ABSTRACT

The terms "on" and "off" were used by Marsden and his contemporaries over 40 years ago to describe times when Parkinson's disease patients experienced good motor function ("on") and immobility ("off"). Yet there remains no published consensus definition of "off", leading clinicians and patients to develop individualized impressions of "off" determinations. In this paper, we first discuss the evolution of the terminology and understanding of "off" states since Marsden's time, which now include non-motor as well as motor symptoms. We then review pathophysiology and risk factors for the development of "off" states as well as tools to detect the "off" state, before proposing a practical definition of "off" for consideration. A common, practical definition of the "off" state could improve clinical recognition of "off" symptoms and lead to significant benefit for patients.

1. Introduction

Levodopa is an effective medication for the motor symptoms of Parkinson's disease (PD), but as the disease advances, all patients develop fluctuations in the control of their symptoms. Marsden described these phenomena approximately 40 years ago in his classic article, "On-Off" Effects in Patients with PD on Chronic Levodopa Therapy [1], in which he wrote that the "essential feature [of 'off'] is a change from mobility to disability." Subtle variations in the severity of PD motor symptoms had already been noted in the literature at that time [2–4], but the sudden transition from good motor function to immobility was termed the "on-off" effect by Sweet and McDowell [5] because it was akin to turning off a light switch. The term "on-off" was eventually applied to those with a slower transition to "off", though Marsden called this gradual decrease of motor benefit from each levodopa dose an "end-of-dose deterioration", which was improved with the next dose of levodopa. This end-of-dose deterioration would lead clinicians to prescribe more levodopa, which progressed over time to "yo-yo-ing" (a term hardly used anymore), when patients would unpredictably swing from an "on" state of good motor function with severe dyskinesias to an "off" state of immobility over a period of minutes and vice versa. End-of-dose deterioration is now more commonly known as the wearing-off phenomenon [6].

The terms "on" and "off" appear so frequently in the literature that clinicians who treat patients with PD are familiar with the concept. Yet, there remains no published consensus definition of "off", leaving each individual clinician and patient with a different interpretation of the term. In this article, we discuss the evolution of the terminology and understanding of "off" states since the

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Marsden publication. We also review pathophysiology and risk factors before proposing a practical definition of "off" for consideration, encompassing clinical experience over the last 40 years.

2. Terminology of "on-off" effects

Motor symptoms have dominated much of the research on PD, so the "on-off" effects from levodopa that Marsden and his contemporaries described are now often referred to as motor fluctuations. Motor fluctuations, "Offs", and dyskinesias are collectively known as motor complications. Because the focus of this article is on "off" states, we will not cover the different types of dyskinesias here. Table 1 describes the various terms used in the literature to describe "off' states [6,7].

Wearing off/end-of-dose deterioration and "yo-yo-ing" have been described above. "On-Off" phenomenon, sudden "off", and random "off" refer to the sudden and sometimes random transition from the "on" to "off" state. Early morning akinesia/bradykinesia describes the morning slowness or immobility experienced prior to the first medication dose of the day. This is typically an "off" state related to low plasma levodopa levels from not taking levodopa during the night. Delayed "on" occurs when it takes longer for a levodopa dose to start working and improve motor symptoms. This is common with the first dose in the morning or after a meal. Alternatively, in some patients, the first dose of levodopa may give the best response for the day with less benefit from subsequent doses. A dose failure or no "on" refers to times when the levodopa dose fails to work. In the literature, all of these terms refer to varying motor symptoms. When sensory or other non-motor symptoms fluctuate and worsen during "off" states, they are typically distinguished from motor "offs" by use of the following terms: sensory "off", behavioral "off", non-motor "off", or non-motor fluctuations [6,8–12].

3. Symptoms of "off"

3.1. Motor

Motor symptoms of the "off" state include rest tremor, bradykinesia, and rigidity. Bradykinesia can manifest as generalized slowness, slowness in any limb, incoordination or reduced dexterity, a sense of weakness or gait difficulty. Other motor symptoms of wearing-off include muscle cramping, difficulty in getting out of a chair or car seat, problems with balance, difficulty in swallowing, hypophonia, shortness of breath, or early morning muscle cramps (or dystonia) in hands, feet or legs. In a review of these and other symptoms tested in the development of a Wearing Off Questionnaire, tremor, slowness, stiffness, muscle cramping, and reduced dexterity were the most specific of the motor symptoms to predict wearing off in PD [13].

3.2. Non-motor

Despite recent studies suggesting that non-motor fluctuations may be as common as motor fluctuations [10], non-motor symptoms remain under-recognized and under-reported as an "off" phenomenon [14]. This may be because many non-motor symptoms occur in both the "on" and "off" state and do not necessarily resolve with dopaminergic treatment. However, several non-motor symptoms improve in the "on" state and worsen or are more prevalent in the "off" state (see Table 2) [12,15]. Non-motor fluctuations can be divided into neuropsychiatric, autonomic and sensory manifestations (see Table 2) [9]. Neuropsychiatric fluctuations are the most common (50% of patients) and encompass such symptoms as fluctuations in cognition, attention, anxiety, depression, and apathy, among others [9,10]. Autonomic symptoms are reported by 24–90% of patients with non-motor fluctuations [10,11], and include sweating, lightheadedness, abdominal pain/bloating, and urinary urgency. Sensory symptoms that fluctuate include visual disturbances, pain, dysesthesia, akathisia and restless legs syndrome, with pain being the most common [9,16]. The majority of patients with non-motor fluctuations have symptoms in all three major domains. Anxiety/panic attacks, mood changes, slow thinking and pain are the most specific non-motor symptoms to predict wearing off in PD [13].

4. Fluctuations and "offs": incidence and risk factors

It is commonly quoted that 10% of patients annually develop motor fluctuations after starting treatment with levodopa [17] and approximately 40% of patients develop motor fluctuations and dyskinesia between 4 and 6 years of treatment with levodopa [18]. However, other studies report that 25–50% of patients develop wearing off within 2 years of starting levodopa [19–21]. In the Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study, the first double-blind parallel-group trial to compare the effect of initiating treatment with different doses of levodopa in patients not requiring dopaminergic therapy, 30% of patients randomized to the highest dose (600 mg of levodopa daily) developed "off" time by the end of the nine month study [21]. Thus the estimated prevalence of wearing off likely varies depending on the definition of motor fluctuations, age of the patient, ascertainment

Table 1
Terms used to describe "Off" states in Parkinson's Disease due to levodopa therapy.

Motor Fluctuations/"Offs"
• Wearing off or end-of-dose deterioration • On-Off phenomenon/Sudden "off"/Random "off" • Yo-yo-ing • Early morning akinesia/bradykinesia • Delayed "on" • Dose failure or No "on" • Weak response at the end of day
Non-motor "offs"
• Sensory "off" • Behavioral "off" • Non-motor "off" • Non-motor fluctuations

*Adapted from Stocchi [6] and Fahn [7].