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Commentary

Winding Back the Clock on Advanced Therapies: It's Time to Get Smart

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Abstract. Our language affects patients' perceptions of therapies. In Parkinson's disease, emergent response fluctuations and dyskinesias typically trigger conversations around commencing an "*Advanced Therapy*" which carries notions of *Advanced Disease*. The patient, resolute in their commitment to fighting the disease, is misled. Chasing reassurance that their disease has not yet progressed considerably; they may therefore resist a potentially life-changing therapy. Instead, we should offer a "*Smart Therapy*". This term more accurately and positively describes therapies on offer that stabilize response fluctuations and improve quality of life, without a focus on the negative connotations of progression to more advanced disease.

Plain Language Summary
The language we use with our patients affects their perception of a therapy on offer and their willingness to take it up. In Parkinson's disease when motor response fluctuations and dyskinesias become extremely challenging and disabling for patients despite medication optimization, it might prompt conversations with the patient in appropriate circumstances about offering an "*Advanced Therapy*" such as deep brain stimulation surgery or continuous infusion pumps. However, from the patient's perspective, putting up a steadfast fight against their disease, this label carries unwanted and misleading connotations of *Advanced Disease.* This can lead to hesitation from taking up these potentially life-changing therapies. Therefore, in this Commentary we propose a rebranding in line with other modern technology like smart phones and smart homes, emphasizing the positive and personalized features of these therapies, and focusing on the goal of stabilizing symptoms and improving quality of life. We should offer patients "*Smart Therapies*". It's time to Get Smart!

Keywords: Deep brain stimulation, advanced therapies, Parkinson's disease, personalized medicine, patient-centered care, levodopa

Levodopa therapy has been the mainstay of pharmacological treatment for persons with Parkinson's disease (PD) for 60 years.[1] However, its *Achilles' Heel* has been the unavoidable emergence of motor and non-motor response fluctuations with disease progression that impose significant functional limitations on patients and impact on quality of life.[2,3] These problems generally become more common and more troublesome as the disease progresses and about half of all patients will experience wearing off and a

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third experience dyskinesias within two years following the initiation of levodopa therapy.[2] In particular, those with young-onset PD are more likely to develop response fluctuations early in the course of levodopa treatment, and much sooner than those with an older disease onset.[4,5] These younger patients are likely to endure a unique impact on social, professional, and family life.[5] Taken together, the highly variable response fluctuations with oral levodopa therapy represent a major management challenge for the clinician and an even bigger challenge for vulnerable patients and their caregivers.

These debilitating problems can be countered at least in part with a variety of device-assisted approaches that have been enabled by advances in technology.[6] These device-aided approaches include deep brain surgery and a variety of pump therapies that deliver continuous pharmacological stimulation. These approaches are also commonly referred to as "*Advanced Therapies*", and this term is used not only during intercollegiate communication between healthcare professionals, but also in communication directed towards patients and their families. The available advanced therapies share a common therapeutic goal of achieving smooth and stable stimulation of dopaminergic circuitries, leading to decreased "OFF" time and a reduction in dyskinesias.[6] All the advanced therapies offer advantages over and above optimizing oral pharmacological therapy, but they have never been compared directly.[7] Each of the available approaches comes with specific advantages but also with particular challenges, which emphasizes the importance of adequate personal counselling and a process of shared decision making based on the latest medical evidence.[8]

Unfortunately, it appears that not all eligible patients ultimately receive one of these device-assisted therapies. There are several possible explanations for this. One is presumably related to the fact that not all physicians who look after persons with PD are fully familiar with these device-assisted therapies, and certainly not with all of them, which restricts the process of individualized medicine and of shared decision making. Another factor is undoubtedly the perceived burden that comes with one of the advanced therapies, which are more invasive than simple oral pharmacotherapy.[9] Caregiver burden may also increase, for example by the demands arising from the daily care of a tube or need to prepare ampoules and cassettes. Also, carrying an infusion device continually confronts patients with the existence of a progressive disease, although the same applies to high-frequency administration of oral levodopa, with or without other antiparkinsonian drugs. These factors may partially explain why many patients are reluctant to increase the daily rate of administration, even if the burden of "OFF" symptoms and fluctuations are evidently influencing their quality of life.

Another relevant factor is a fear of treatments in general. A good example in this regard is the ever-persisting *Levodopa Phobia,* such that some clinicians and patients prefer to delay the initiation (or an adequate dose increase) of levodopa therapy, in the hope of delaying the onset of levodopa-related fluctuations. Such decisions may also be driven by the false notion that levodopa might accelerate disease progression.[10] The latter misconceptions have largely been dispelled in a double-blind placebo-controlled delayed-start trial in which disease progression and rates of response fluctuations did not differ between late- and early-start groups.[11,12]

Importantly, this treatment phobia also extends to other forms of management and is likely to impact the patient's decision to start an advanced therapy. Indeed, the reluctance among patients to initiate a new therapy, effective as it may be, is in part explained by their understandable desire to resist surrendering to a progressive neurodegenerative disorder.[10] Said differently, consenting to start a new additional therapy is felt by many patients as an implicit acknowledgement that their disease has progressed substantially and, along the same lines, that by denying such an advanced therapy, they can reassure themselves that their disease has not yet progressed considerably. In that regard, it has been our experience that use of the term "*Advanced*" therapies (logical as it may be from the perspective of professionals who understand the technological innovations that drive these therapies) actually may have a counter-productive effect, in that it inadvertently confronts patients with their underlying disease progression. When we debriefed with patients in clinic who wished to postpone the advanced treatment, they informed us that this decision was driven at least in part by the fact that the term "*Advanced Therapy*" was loaded with inextricable connotations of advanced disease. This label is viewed by patients as pejorative and misleads patients to feel that as if by taking up these interventions, they are conceding irreversibly to a relentless progression to the advanced stages of disease.[13,14] This inadvertently layers an iatrogenic barrier in patient psychology, leading to an unbased hesitation from engagement especially when added to rational

factors such as invasiveness and the potential adverse effects that patients are already evaluating. It is therefore essential to explore what drives patients in their decision to choose or even reject a particular treatment. As such, words matter, and may make an enormous difference in convincing patients and caregivers to take the right step. To achieve this, it takes time—frequently more than one clinical appointment—and commitment, using the right words, guarding the autonomy of the patient, but also guiding him or her in making the right decision.

So, what's in a name? Have we created an *Advanced Therapy Phobia?* And what is the impact of implying or even explicitly announcing that a more advanced stage has been reached, particularly now that device-assisted therapies are increasingly considered earlier in the disease course.[11,12] The language we use with our patients matters and may affect decision making. Patients have a strong preference for shared decision making in the process of initiating advanced therapy and being aware of all treatment options is highly important to them.[8] Rather than offering an "*Advanced Therapy*", layered with the stigma of advanced disease and misguided hopelessness fueling patient hesitancy, we should be offering our patients "*Smart Therapies*" that emphasize evidence-backed optimism toward maintaining a high level of independent functioning and quality of life in a way that oral pharmacotherapy cannot.

This proposed 'rebranding' of the name "*Advanced Therapies*" aims to provoke thinking. We acknowledge there might be alternative options and that different languages may require a different terminology. We are obviously open to hearing about alternative suggestions. In the meantime, we do favor the term "Smart" as it adequately captures the smart nature of the device-assisted therapies which are dynamic and can be modulated in an on-demand fashion much like other smart technologies that are prevalent in our households and daily lives, such as smart phones, smart watches, or smart fridges. "*Smart Therapies*" is also future-proofed and extends to encapsulate novel and developing therapies such as adaptive deep brain stimulation, directional and multifocal deep brain stimulation, continuous device-assisted therapies with novel formats and routes of administration, lesional therapies such as MRI guided focus ultrasound and radiofrequency thermocoagulation, gene therapy and cell-based therapies.[6,9,15–17] Furthermore, there is evidence that switching between these smart therapies or introducing a second one may be beneficial, depending on symptoms and evolving patient factors and preferences, yielding comparable clinical benefits as when introducing the first.[18] This, in combination with the accelerating development of novel technologies and a growing population of patients who can benefit from these, places the field at a timely juncture to consider a much-needed rebranding of our terminology and to empower our vulnerable patients at a tipping point in their disease process to benefit from a life changing and enabling therapy. In short, it is time to *Get Smart*!

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