Movement Disorders
CLINICAL PRACTICE

EDITORIAL COMMENTARY

Unmet Needs in Parkinson's Disease

Susan H. Fox, MD, PhD[1,*] *and Francisco Cardoso, MD, PhD*[2]

Despite decades of research and an increased understanding of the pathophysiology of Parkinson's disease (PD), there are many aspects of the disease that remain challenging and difficult to manage in daily clinical practice. As clinicians, we all see the remarkable benefits of levodopa (L-dopa) replacement on motor and some nonmotor symptoms, but equally there is lack of benefit on many of the more disabling issues that patients experience, including nonmotor aspects, gait, and balance. The inability we have to slow down disease progression means that the management of many PD symptoms is effectively "palliative," and our ability to deliver such care is challenged often more by geopolitical issues than a lack of knowledge of what is required. Finally, the advent of artificial intelligence (AI) is leading to its own "unmet need" with a better requirement for the validated use of this powerful technology to potentially aid diagnosis, management, and research into PD. The First International Parkinson and Movement Disorders Society (MDS) *Movement Disorder Clinical Practice* conference highlighted and challenged us to continue to address these unmet needs.

L-Dopa Nonresponsive Symptoms in PD

The heterogeneity of PD symptoms means that personalized and targeted medicine is the key to helping an individual with PD. Many symptoms of PD respond very well to dopaminergic agents, especially the motor symptoms, and remain effective with dose and timing adjustments over many years. The many nonmotor symptoms associated with PD are often less effectively treated with dopaminergics and thus are a significant unmet clinical need. Antonini and colleagues[1] reviewed this and emphasized both the multisystem nature of PD and the need to focus on nondopaminergic therapies. Nonmotor symptoms can begin early in the disease course and manifest before motor symptoms, including rapid eye movement sleep behavior disorder. However, most nonmotor symptoms occur with disease progression as a result of pathological changes in nondopaminergic systems and emphasize the multisystemic nature of PD. One of the most disabling is cognitive decline, which can begin early in the course of PD, with mild cognitive impairment leading to dementia and psychosis in some individuals. In addition to Lewy body pathology, coexistent pathologies, such as vascular disease and Alzheimer's disease, add to the burden with additional clinical symptoms and expand the need for multiple targeted treatment options. Mood issues, autonomic failure, pain, and sensory symptoms include many other symptoms that are either not or less L-dopa responsive. It is also increasingly recognized that subsets of patients with PD have predominantly nonmotor symptoms and thus non–L-dopa-responsive symptoms that can result in a faster progression of the disease. Despite the recognition of nonmotor issues in PD as the most bothersome and disabling for patients with PD, there remain many symptoms that have either no or limited treatment options. Until an effective disease-modifying therapy to slow disease progression in PD becomes clinically available, there needs to be a concerted effort and focus on improving the management of nonmotor issues in PD. This includes collaboration with other medical disciplines such as psychiatry, gastroenterology, urology, and cardiology among others and prioritized funding support of research into these symptoms.

Gait Impairment in PD

A motor issue in PD that also remains an unmet need is impaired gait and balance with falls among the common sequalae. Gait and balance are another set of symptoms in PD that may be, or eventually become, L-dopa resistant.[2] Tossermans et al helpfully separated gait disorder into 2 clinically recognizable categories: continuous-gait disorders of PD with typical features of slow speed, short steps, and a reduced arm swing with disease progression compared with episodic-gait disorders such as intermittent festination and freezing of gait. The management of these 2 types may differ. Some components of continuous gait impairment such as speed of gait may initially respond to L-dopa, but the effectiveness on the quality of walking becomes less effective over time. Progressive nondopaminergic pathological regions

[1]*Movement Disorder Clinic, Edmond J. Safra Program in Parkinson's Disease, Division of Neurology, University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada;* [2]*The Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil*

***Correspondence to:** Dr. Susan Fox, Movement Disorder Clinic, Toronto Western Hospital, 399, Bathurst St, Toronto ON, M5T 2S8, Canada; E-mail: susan.fox@uhnresearch.ca
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become implicated in gait and balance dysfunction and alternate pharmacological targets may be tried, including cholinergic and adrenergic targets. Intermittent disruptions of gait are usually less responsive or nonresponsive to L-dopa as well as being unpredictable, and management is thus better targeted at more nonpharmacological approaches. The authors highlighted this approach, termed "compensatory strategies," where patients learn tricks and maneuvers that enable them to overcome some of the common issues of freezing. A key feature is that such strategies need to be tailored to the individual needs of the person. A range of compensation strategies have been reviewed and categorized by the authors, including external and internal cueing, weight shifting/changing style of walking/altering the mental state such as reducing anxiety, and alternatives to walking such as riding a bicycle. Maximizing the education of these strategies to the wider PD population by use of a visual tool is a strategy that may help people "learn" what can work for them.[2] The individual ability to use internally generated strategies appears to be better than external cues and reinforces the individualization of strategies to overcome freezing. Accessibility of expertise in education of patient and health care professionals is key to the increased adoption of these tools, but the increased use of the virtual delivery of care now enables improved education, and the hope is that such an important tool will assist with managing the very common "unmet" need of gait and balance issues in PD.

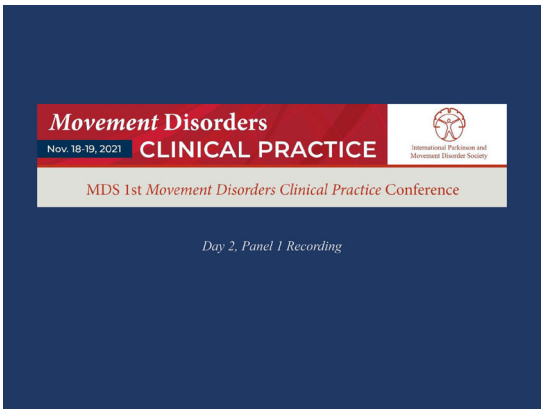
Palliative Care in PD

Although their life expectancy is still lower than the general population, people with PD live much longer than in the past. The late stage of the disease is often dominated by motor and nonmotor features resistant to available medical and surgical treatments. In this context, palliative care is of essential importance. Hvisdak et al[3] provided a good overview of palliative care in PD, describing what they believe to be general pillars likely applicable at a global level. However, end-of-life perception is widely variable depending on the cultural background of the individual. There are several unmet needs related to palliative care in PD and related disorders.[4,5] One of them is the development of strategies that consider different geographic, economic, and cultural realities. A second problem is the limited access to palliative care at a global level. Sadly, this is even true in developed countries. A final vexing issue is that movement disorders professionals and providers of palliative care often lack knowledge of the others' area. Given its importance and the complexities of the management of therapeutics of PD, it is mandatory to launch a global effort to develop individualized palliative care strategies, improve access to them, and offer education to all professionals providing health care to people with PD and related disorders. Fortunately, the MDS is fully committed to this endeavor. The society has created a Palliative Care Study Group that has been actively working to address these unmet needs.[6]

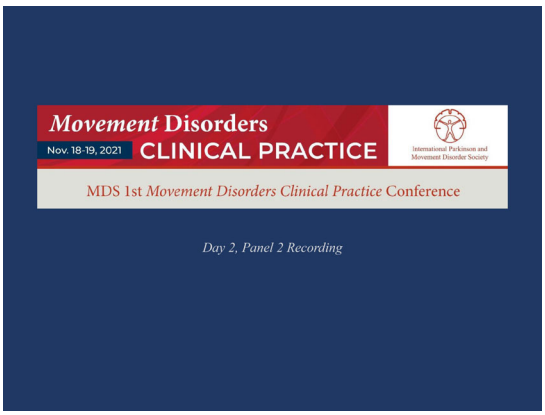
Digital Technologies in PD

Jha et al[7] provided an astute critical view of digital biomarkers in PD. The advance of digital technologies and particularly AI has generated the idea that these tools will play a major role in providing care to people not only with PD but also diseases in general as well as improving the quality and efficiency of clinical trials. As the authors elegantly demonstrated, there are many challenges ahead before these expectations come true. PD is a multidimensional condition with a wide array of interplaying complex motor and nonmotor features that result in a subjective feeling of quality of life. Tools that conform to the "single digital biomarker hypothesis" often, if not always, fail to capture the complexity of PD and related disorders. If these flawed biomarkers are adopted as endpoints in clinical trials, they will generate information that bear little relationship with the quality of life of patients. Of note, there are already ongoing studies looking into clinimetric properties of digital applications in PD.[8] Before they are adopted, it is mandatory that these tools are carefully scrutinized as to their validity and correlation with patient-reported outcomes (PROs). It is comforting that regulatory agencies have soberly and critically assessed these new technologies, requesting demonstration that their measurements are correlated with PROs.[9] Paradoxically, many of the digital technologies in development generate a large number of data that do not provide meaningful information about the function of the patients, leading to the problem of "missing the forest for the trees" as stated by Jha and colleagues.[7] Finally, given the growth of the presence of digital technologies and AI in human lives, it is fair to assume that they will be part of the care of people with PD and related disorders. However, whatever their future in Medicine, they must be an addition to, not a substitution for, the irreplaceable in-person encounter of a patient and a health care professional.

In conclusion, the First Movement Disorders Clinical Practice Conference provided an in-depth diagnosis of unmet needs in PD, showing that they encompass a large number of motor and nonmotor issues as well as access to palliative and other modalities of care. Fortunately, all authors described proposals to overcome these unmet needs. Finally, the current limitations and advantages of digital technologies were also discussed at the conference, with a realistic proposal of how to move forward with the development of a multidimensional digital diary for people with PD (Video 1 and 2).



Video 1. *Movement Disorder Clinical Practice* panel, day 2. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13838



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