CLINICAL MANAGEMENT OF DRUG-INDUCED DYSKINESIA IN PARKINSON'S DISEASE: WHY CURRENT APPROACHES MAY NEED TO BE CHANGED TO OPTIMISE QUALITY OF LIFE

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ABSTRACT

Parkinson's disease is a complex, progressive neurodegenerative disorder associated with both motor and non-motor symptoms. Current treatment strategies mainly target the alleviation of motor symptoms through dopaminergic replacement therapy. Many patients with Parkinson's disease will eventually experience motor complications associated with their anti-parkinsonian medication. One of those complications is drug-induced dyskinesia. This paper firstly reviews current approaches to the management of drug-induced dyskinesia, from modifications to the titration of medication, to more invasive approaches like deep brain stimulation. Following this we describe a recent proposal suggesting that the treatment of dyskinesia should be based on the impact on daily activities of patients rather than on the mere presence of the condition. Next, we discuss how this approach could improve the quality of life of patients and their caregivers and finally, we suggest possible ways of implementing this approach in practice.

Keywords: Levodopa-induced dyskinesia, quality of life, caregiver, monitoring.

INTRODUCTION

Parkinson's disease (PD) is a complex, progressive, neurodegenerative disorder associated with multiple neuropathological dysfunctions. One of its features is the degeneration of dopaminergic neurons within the basal ganglia leading to the hallmark motor symptoms of PD: tremor, bradykinesia/akinesia, rigidity, and postural instability.[1] To counteract the deleterious effect of dopamine depletion, dopamine replacement therapy is usually initiated in the early stages of the disease. However, neurophysiological alterations related to disease progression and prolonged use of dopaminergic agents often leads to drug-induced dyskinesia. Within 5 years of dopamine replacement therapy initiation (levodopa), 30–50% of patients report experiencing dyskinesia;[2,3] by Year 10 of treatment, 60–100% of patients report dyskinesia.[2,4] Although there are different manifestations of dyskinesia, the most common type of drug-induced dyskinesia in PD is choreic peak-dose dyskinesia.[5] Dyskinesias are characterised by random, non-rhythmic (in appearance), and unsustained involuntary movements that can be present throughout the body.[6] Dyskinesia can lead to diminished quality of life for both patients and their caregivers, and create an additional burden on the healthcare system. Several approaches may be undertaken by clinicians to control dyskinesia while maintaining clinically significant reductions in typical PD symptoms. In this paper, we first provide

an overview of the current approaches in managing dyskinesia. We then discuss a novel approach to the management of dyskinesia that we have recently put forward, how this approach could improve the quality of life of patients, and how it could be implemented within practice.

CURRENT APPROACH

Many clinicians treating a PD patient exhibiting dyskinesias will promptly attempt to reduce their amplitude using one of the following approaches:

Modification of Dopamine Medication Titration

While the primary option for management of dyskinesia is to reduce medication dosage, this can lead to the resurgence of parkinsonian symptoms. Hence, this option is not viable for many patients as most prefer to experience mild dyskinesia than to become 'immobilised' by their symptoms. Another option available to clinicians is the fractionation of medication doses. This method maintains the overall daily dose of medication by having patients take smaller doses of medication at shorter intervals during the day. The theory behind this approach is to reduce the pulsatile nature of medication intake resulting in more stable levels of dopamine within the system. However, this method often provides adequate management of dyskinesia for a limited time only and is effective in only some patients. This has led some to try controlled-release formulations of medication.[7] While this in theory could help in the management of dyskinesia by further reducing the pulsatile nature of medication intake, very little scientific evidence supports its use in clinical practice.[8]

Dopamine Agonists

Another option available to clinicians is the co-administration of dopamine agonists.[9] The idea behind this approach is to provide relatively low doses of both medications thus minimising the possible occurrence of side effects. However, the effectiveness of such an approach in reducing dyskinesia is very sparse at best.[8] Additionally, dopamine agonists are associated with more non-motor side effects than levodopa and it has been previously shown that some patients on dopamine agonist monotherapy can also develop dyskinesia.[10]

Continuous Drug Delivery (Duopa™/Duodopa; Apomorphine)

Building on the theory that reducing the pulsatile delivery of medication will minimise dyskinesia, continuous drug delivery systems such as duodenal infusion of levodopa have been developed. Previous studies have demonstrated the efficacy of this approach in reducing the duration of dyskinesia.[11,12] Similarly, continuous subcutaneous apomorphine infusion has been shown to significantly reduce dyskinesia.[13] These approaches however require a complex procedure and extensive long-term monitoring to limit the potentially severe complications. As such, this treatment option may not be suitable for many patients and may indeed add to the burden faced by patients and their caregivers.

Amantadine

Since previous studies have demonstrated a link between the overexpression of N-methyl-D-aspartate (NMDA) receptors and dyskinesia, another option available to clinicians is to provide adjunctive NMDA antagonist medications to patients. According to the European Federation of Neurological Societies (EFNS) guidelines, amantadine (200–400 mg/day) has a Level A recommendation for the management of levodopa-induced dyskinesia.[14] Amantadine has been shown to significantly reduce the duration of dyskinesia[15] while simultaneously providing a mild anti-parkinsonian effect.[16] However, many patients' response to amantadine is fleeting and thus its use provides only temporary relief. Recently, an extended release formulation of amantadine has been introduced and shown to be effective with minimal side effects at a daily dose of 340 mg.[17]

Serotoninergic Agents

Given the close relationship between the dopaminergic and serotoninergic systems within the basal ganglia, there have been some investigations into the use of serotoninergic medication to control dyskinesia. Clozapine, a high-affinity serotoninergic agonist, was shown to significantly reduce dyskinesia.[18] However, its severe side effect profile requires intensive monitoring thus greatly limiting its use. Many preclinical studies targeting the serotoninergic system yielded promising results, however clinical trials assessing the efficacy of 5-HT_{1A} receptor antagonists such as buspirone[19-21] or sarizotan[22] failed to demonstrate an improvement of levodopa-induced dyskinesia and even led to the worsening of parkinsonian symptoms.[23] Nonetheless, there is currently an ongoing clinical trial of buspirone for the management of dyskinesia (NCT02617017). To optimise the efficacy of this treatment strategy, a current

clinical trial is examining the use of combined buspirone and amantadine for the management of levodopa-induced dyskinesia (NCT02589340). Other serotoninergic agents such as fluoxetine[24] have also been shown to be moderately effective in managing dyskinesia. More recent observations encourage the use of combined 5-HT_{1A} and 5-HT_{1B} receptor antagonists, such as eltoprazine, and suggest the use of serotonin transporter (SERT) inhibitors as an alternative target.[25]

Surgical Interventions

In severe cases where dyskinesias are refractory to drug management, surgical options may be considered. Deep brain stimulation of the globus pallidus internus and subthalamic nucleus have been demonstrated to significantly reduce dyskinesia by ≥80%.[26,27] While some of this improvement may be linked to a reduction in medication dosage after surgery, electrical stimulation of these targets is thought to induce antidyskinetic mechanisms. However, several restrictions associated with age, cognition, and psychiatric symptoms limit the use of these interventions. Lesions of the globus pallidus internus and subthalamic nucleus have also been shown to significantly improve drug-refractory dyskinesia.[28,29] Yet lesions may only provide unilateral dyskinesia alleviation, as bilateral procedures are associated with significant complications.

CLINICAL QUANDARY

While the aforementioned interventions can provide a variable degree of reduction in dyskinesia amplitude and duration, one question clinicians should be asking themselves is whether it is always a necessity to treat dyskinesia. Previous studies have demonstrated that dyskinesia may not be related to quality of life in PD.[2,30-32] This may be because dyskinesias do not affect every patient in the same way. It was recently proposed that the decision to treat should not be based on the presence or absence of dyskinesia but rather on the impact on the motor repertoire available to patients.[5] This idea stemmed from several studies demonstrating that dyskinesia and other motor symptoms of PD did not impair the performance of every type of voluntary movement. In other words, the impact of dyskinesia was closely related to the amplitude and velocity of the task being performed. As such, dyskinesias will have a deleterious effect on patients' quality of life only if their motor repertoire (the activities that they usually perform daily) is altered by the condition. Since not every person requires the same motor repertoire in their daily life, the decision to treat would need to be personalised to each patient. For instance, a seamstress required to perform very fine movements for her daily occupations may require a change in treatment to manage even very mild dyskinesia despite good alleviation of parkinsonian symptoms (Figure 1, Case 1). Conversely, a patient whose dyskinesia does not interfere with his/her daily activities, because they mainly involve gross motor tasks or because the dyskinesias occur at a time of day when fine motor movements are not as essential, may not require immediate changes to his/her treatment regimen that otherwise satisfactorily manages his/her symptoms (Figure 1, Case 2).

One of the main issues with such an approach is that clinicians can only observe dyskinesia during a very narrow time window when patients are in the clinic. They must then rely on patient reports which are highly unreliable as their perception can be altered due to the disease. We have observed patients reporting no dyskinesia whilst exhibiting constant dyskinesia lasting several hours when they visited the laboratory; this has been presented on multiple occasions. Conversely, we have also observed patients that have communicated having severe impairments due to dyskinesia and exhibited no involuntary movements throughout several 4 to 5-hour monitoring periods. Therefore, new evaluation methods need to be implemented to capture the changes in motor repertoire and identify whether they are detrimental to patients' quality of life (Figure 2).

WHAT WOULD BE THE BENEFITS OF SUCH AN APPROACH?

Quality of Life

The impact of dyskinesia on quality of life is still being debated. For instance, a recent study by Hechtner et al.[33] found that dyskinesia, whether peak-dose or biphasic, did not have a significant impact on quality of life as assessed by the 39 item Parkinson's Disease Questionnaire (PDQ-39)[34] and EuroQol five dimensions questionnaire (EQ-5D)[35] criteria. Similarly, Martínez-Martin et al.[36] found that motor complications such as dyskinesia, as assessed by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part IV,[37] did not exhibit a significant influence on health-related quality of life. Fereshtehnejad et al.[38] also did not observe any significant influence of

dyskinesia on quality of life. On the other hand, Soh et al.[39] have observed that impairments in motor function, as assessed by the MDS-UPDRS Part IV,[40] contributed directly to health-related quality of life as well as indirectly through limitations in self-care. Likewise, Wu et al.[41] observed that motor complications such as dyskinesia had a significant impact on quality of life. Specifically, they demonstrated that motor complications were a significant, albeit minor, determinant of the PDQ-3934 summary index as well as the activities of daily living.

So why is it that some studies find that dyskinesia are detrimental to the quality of life of patients with PD, while others do not? It is possible that this may stem from the clinical characteristics of the sample populations. Some studies, such as that from Martínez-Martin et al.,[36] had participants with very little dyskinesia. It is therefore more likely that the dyskinesias do not interfere with their quality of life at a group level. On the other hand, it may also be that in other studies where dyskinesias have been shown to have a deleterious effect on quality of life, it was through an indirect path. For instance, Soh et al.[39] and Wu et al.[41] both observed that dyskinesia had a negative effect on activities of daily living. More specifically, Hechtner et al.[33] observed that peak-dose dyskinesia had a significantly negative impact on activities of daily living. This is in direct relation to our proposed approach, where treatment should be based on the impact of dyskinesia on the motor repertoire of patients. In Case 1, the daily activities of the patient are hampered by the presence of dyskinesia. As such, this would inextricably lead to a reduction in quality of life. In Case 2 however, the presence of dyskinesia does not affect the motor repertoire of the patient. As such, his/her quality of life would also not be affected. Soh et al.[39] demonstrated that limitations in performing activities of daily living was one of the strongest contributing factors to diminished health-related quality of life. Similarly, Fereshtehnejad et al.[38] demonstrated a significant influence on the activities of daily living as assessed by the MDS-UPDRS Part II,[40] on the summary index of the PDQ-3934 (overall quality of life), but also on specific domains of quality of life such as mobility, activities of daily living, stigma, social support, cognition, and communication domains. By only modifying the drug regimen of patients whose motor repertoire is altered we may be able to optimise the improvement in quality of life concomitantly, minimising the burden associated with the titration period of new medication that may temporarily negatively impact the quality of life of patients.

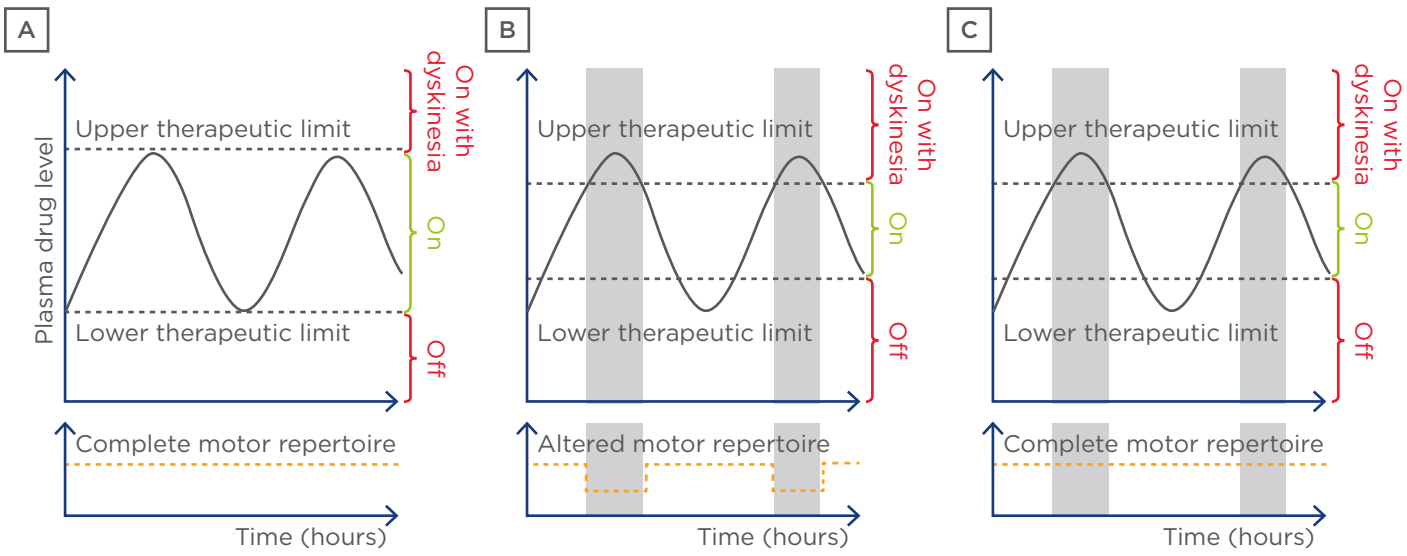

Figure 1: Graphical representations of various contexts of levodopa plasma fluctuations.
A) Honeymoon period: Fluctuations in levodopa plasma level from the onset of treatment, and the motor repertoire available to patients. B) Case 1: Short-term variations in levodopa plasma levels associated with motor fluctuations, and changes in motor repertoire as the therapeutic window narrows. C) Case 2: Short-term variations in levodopa plasma levels associated with motor fluctuations but without any changes in motor repertoire as the therapeutic window narrows.

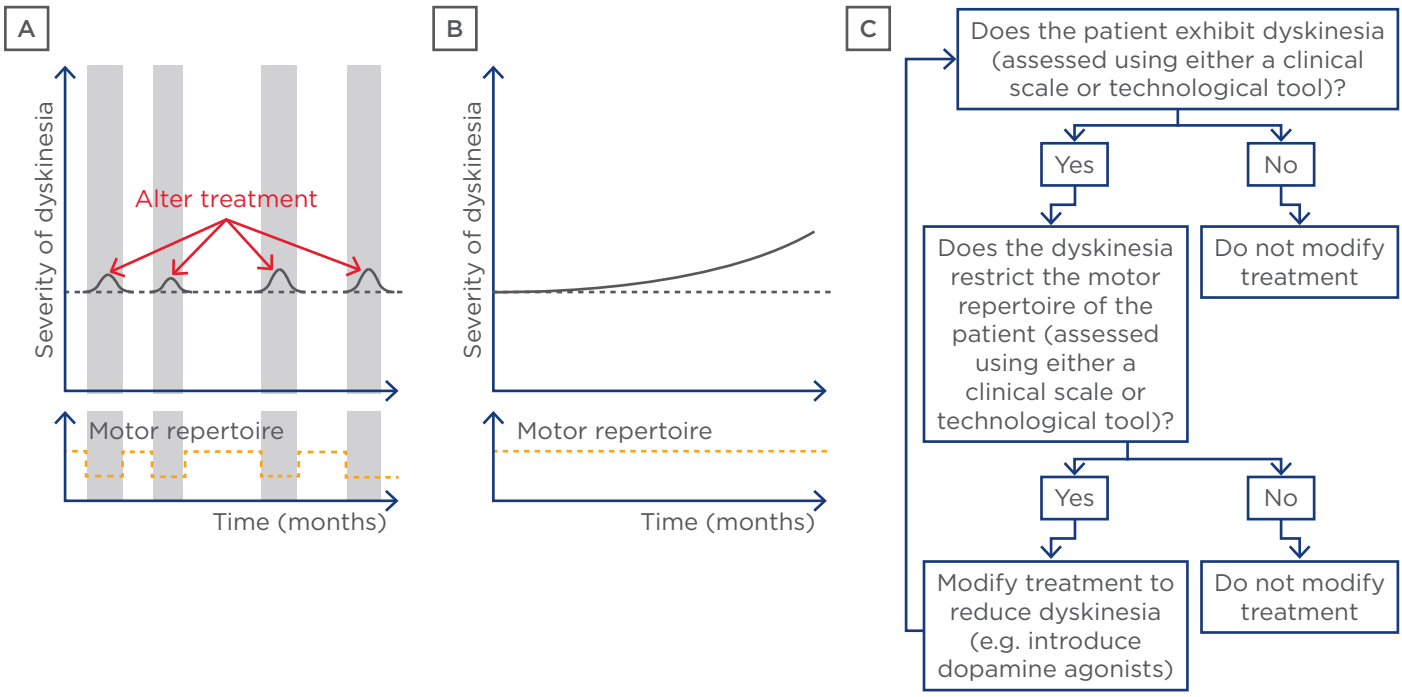

Figure 2: Graphical representation of the long-term variations in the severity of dyskinesia.
A) Case 1: Long-term variations associated with alterations in motor repertoire that warrant a change in treatment. B) Case 2: Graphical representation of the long-term changes in dyskinesia severity that does not alter the motor repertoire and thus does not require a modification in therapy. C) Proposed decision algorithm for the management of dyskinesia.

Caregiver Burden

Few studies have examined the impact of dyskinesia on caregiver burden. Some have observed that the presence of dyskinesia or motor complications were not associated with an increased caregiver burden. Agrawal et al.[42] observed that although there was a very mild significant correlation between dyskinesia and caregiver quality of life, dyskinesias were not a significant predictor of caregiver burden or quality of life. Oguh et al.[43] observed, in a large cohort of >2,000 caregivers of patients with PD, that those exhibiting more severe strain were caring for patients with PD that had a higher incidence of motor fluctuations. However, in a regression analysis, motor complications were not a significant predictor of caregiver strain. Leroi et al.[44] observed that motor complications, as assessed by the MDS-UPDRS Part IV, were not significant predictors of caregiver quality of life. On the other hand, Martínez-Martin et al.[45] observed that motor complications, combined with disease duration and disability, were significantly related to caregiver burden, anxiety, and depression. Similarly, Ozdilek and Gunal[46] demonstrated that caregiver burden was significantly affected by the presence of dyskinesia and their impact, as assessed by the MDS-UPDRS Part IV. As such, it seems that the presence of dyskinesia variably impacts quality of life and may not be a very strong predictor of caregiver burden. However, functional limitations in activities of daily living seem to consistently play an important role in caregiver burden. Ozdilek and Gunal[46] also observed that caregiver burden was significantly associated with impairments in activities of daily living of PD patients, as assessed by the MDS-UPDRS Part II. In a meta-analysis, Lau and Au[47] demonstrated that the significant impact of functional limitation in activities of daily living on caregiver burden was greater than that of mood problems and cognitive impairment.

Taken together, this indicates that limitations in activities of daily living, rather than the mere presence of dyskinesia, is of greater importance to the quality of life of patients and their caregivers. Implementing changes to treatment regimens based on the impact of dyskinesia on activities of daily living, comprising the entire motor repertoire of patients with PD, may therefore lead to better quality of life of both patients and their caregivers, as well as alleviating caregiver burden.

HOW COULD THE PROPOSED APPROACH BE IMPLEMENTED?

The most common approach to assessing dyskinesia in patients with PD is to use clinical scales. Several scales are available to clinicians to assess dyskinesia (Table 1). For instance, Part IV of the MDS-UPDRS[37] contains two questions related to the frequency and impact of dyskinesia. Other scales are entirely dedicated to the evaluation of dyskinesia in PD. The Abnormal Involuntary Movement Scale (AIMS)[48] assesses limb-specific location of dyskinesias as well as their intensity. The Unified Dyskinesia Rating Scale (UDysRS)[49] and the Rush Dyskinesia Rating Scale (RDRS)[50] both objectively assess the impact of dyskinesia on activities of daily living. The UDysRS also reports patients' perception of the impact of their dyskinesia. The Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS)[51] and the Parkinson Disease Dyskinesia Scale (PDYS-26)[52] also report patients' perceptions relating to the impact of dyskinesia on specific daily activities. Interestingly, a recent study demonstrated that measures comprising patients' perception (i.e. UDysRS, LFADLDS, and PDYS-26) detected an effect of treatment with amantadine while the MDS-UPDRS-IV, AIMS, and RDRS did not.[53] Furthermore, Goetz et al.[53] observed that the UDysRS provided the largest effect size, indicating that the combination of objective measures of dyskinesia and subjective patient perceptions could best capture the impact of changes in treatment. Utilising scales that examine the impact of dyskinesia on activities of daily living, both objectively and subjectively, may lead to better treatment decisions for patients with PD. Although the scales mentioned previously can provide the impact of dyskinesia on common activities of daily living, they may not cover the entire motor repertoire of patients with PD. As such, the development of new scales, or amendment of currently used scales, may provide even better information to decide when a change in treatment should be explored to manage dyskinesia. For instance, adding elements to current scales that relate to a more complete motor repertoire and that include components similar to those observed in for example the Motor Activity Log (MAL),[54] where both quantity and quality of movements are assessed simultaneously, may provide a better picture of the overall impact of the dyskinesia and indicate whether a change in treatment strategy is warranted.

Finally, recent advances in wearable technology enable low-cost, unobtrusive data collection spanning several hours to days. In combination with advanced mathematical analytics, this technology can identify dyskinesia during specific tasks[55-58] and even within uncontrolled ambulatory settings.[59-61] While more work is required to implement the use of wearable technology in clinical practice, this technology may soon help inform clinicians about the duration and severity of dyskinesia within the patients' living environment as well as the impact on patients' motor repertoire. For example, instead of patients taking their medication at predefined intervals, data collected from body-worn sensors may be used to indicate when patients should take their medication based on the longitudinal monitoring of their motor behaviour.

Table 1: Characteristics of the dyskinesia rating scales.

	Evaluation	Time to complete (years)	Type	Specific to dyskinesia	Assessment period
MDS-UPDRS IV	Frequency + Impact	5	SR	Yes	1 week
AIMS	Limb-specific severity	15	C	No	During visit
UDysRS	Impact on ADL	15	SR + C	Yes	1 week
RDRS	Severity during ADL	5	C	Yes	During visit
LFADLDS	Disability during ADL	5	SR	Yes	A few days
PDYS-26	Impact on ADL	10	SR	Yes	1 week

MDS-UPDRS IV: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part IV; AIMS: Abnormal Involuntary Movement Scale; UDysRS: Unified Dyskinesia Rating Scale; RDRS: Rush Dyskinesia Rating Scale; LFADLDS: Lang-Fahn Activities of Daily Living Dyskinesia Scale; PDYS-26: Parkinson Disease Dyskinesia Scale; ADL: activities of daily living; SR: self-report; C: clinical evaluation.

Feedback could be provided through a simple smartphone application. This may optimise responses as well as reduce motor fluctuations, such as those caused by dyskinesia. This will enable physicians to personalise treatments on a patient-specific basis.

CONCLUSION

As the management of motor symptoms of PD leads to motor complications such as dyskinesia, there is a need to ask whether these complications need to be controlled at all costs in every patient. The shift towards personalised medicine should also be applied in the management of drug-induced dyskinesia. Rather than modifying a treatment approach that is otherwise efficacious in managing motor symptoms, the decision to address dyskinesia by modifying the treatment regimen should be based on the impact of dyskinesia on the motor repertoire of patients and not solely on its presence. We believe that this will improve the quality of life for patients in the long-term, lessen caregiver burden, and alleviate some of the financial burden on the healthcare system. To adequately implement such an approach, there needs to be further developments in how patients are evaluated. Whether it is through the development of new or amended clinical scales, or the use of wearable technology to monitor patient symptoms in their natural environment, collaborative work between clinicians, engineers, and scientists will enable us to move forward more quickly in personalising care and improving the quality of life for patients with PD.

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