# Can Objective Measurements Improve Treatment Outcomes in Parkinson's Disease?

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## Abstract

Many examples in medicine show that therapies are most effective when measurement is used to guide their implementation, dose and effects. There are effective symptomatic therapies for the motor symptoms of Parkinson's disease, which improve quality of life and have a health economic justification for their subsidisation. As measurement should lead to more effective deployment of these therapies, even in a percentage of cases, then costs of therapy would be reduced and by that percentage. We conclude that there is a clear need for continuous objective measures of dyskinesia and bradykinesia while patients go about their normal daily activities. The benefit of measurement would be greatest if these measures were directed at treating fluctuations.

## Keywords

Parkinson's disease, bradykinesia, dyskinesia, fluctuations, measurement, treatment, scales, accelerometry, outcomes, compliance

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'You can't manage what you can't measure' is a well-acknowledged maxim attributed variously to Peter Drucker, W Edward Demming and Bill Hewlett (of Hewlett Packard), but was probably first expressed by Lord Kelvin, the British scientist associated with, among other discoveries, the first and second law of thermodynamics. It is a concept well entrenched in medicine, as attested by the measuring of blood glucose, blood pressure, renal function, etc. to manage their related disorders. It seems likely therefore that measurement would aid in the management of Parkinson's disease (PD). However, it is worth recalling that in clinical management, measuring is only useful if it leads to a decision (usually a therapeutic decision) and to do that the measure should correlate closely with the desired consequence of the decision.

With regard to the second point, measuring blood glucose in diabetes is successful because it directly reflects treatment with insulin, and elevated blood glucose causes long-term pathology. However, the terms diabetes mellitus come from a time when the condition was recognised by 'too much urine' and 'honey in the urine'. Many disorders have passed through a stage where they can only be recognised by symptoms, before measures reflecting the underlying pathology are devised. James Parkinson identified some of the classic motor features of PD, but it was objective measurements with hand dynamometers that helped Charcot to dismiss the idea that PD, at the time known as paralysis agitans, was characterised by weakness and to stress that a core symptom was slowness.[1] In the 1980s, David Marsden[2] pointed out that bradykinesia is the major underlying instigator of many of the motor manifestations of the disorder. Although it is now recognised that PD is much more than a motor condition and has many other features of frontal lobe dysfunction[3] and involves peripheral,[4–6] as well as central widespread neuropathology,[7] recognition of motor symptoms are essential for both diagnosis and disease management. Non-motor symptoms may require treatment to be revised, but the decisions to start treatment, to add a different class of drugs, to alter the number of daily administrations or to consider advanced treatment with deep brain stimulation (DBS) or continuous pump treatments are invariably triggered by motor symptoms. The available therapies for the non-motor symptoms of PD are few and not well studied. By contrast, effective symptomatic treatment of motor symptoms has been available for over 50 years and improved motor function is generally associated also with improved non-motor symptoms, so if 'measuring is only useful if it leads to a therapeutic decision' then measuring the motor symptoms of PD has a higher likelihood of improving treatment outcomes in PD than measuring non-motor symptoms. The rest of this review will therefore concentrate on the question of whether objective measurements of motor symptoms can improve treatment outcomes in PD.

## Does Treating Motor Symptoms Affect Outcomes?

The four cardinal motor symptoms of PD, bradykinesia, rigidity, tremor and postural instability,[8,9] are all considered to reflect dopaminergic failure and are therefore targets of dopamine replacement therapy.

There is consensus that dopaminergic stimulation is effective in controlling bradykinesia, the key symptom of PD,[10] and to a lesser extent tremor and rigidity.[8,11] A good response to dopamine stimulation supports the diagnosis of idiopathic PD and a lack of response implies a less favourable prognosis. Opinions are divided between early intervention and intervening later when symptoms are sufficient to interfere with daily activities and/or lifestyle. The interventionists have concluded from reviews of the evidence[12–18] that bradykinesia causes morbidity and that medications, levodopa (L-DOPA) in particular, have a low incidence of side effects in this early stage. Pragmatists on the other hand, argue that there is no Class 1 Cochrane evidence[19,20] for early intervention, so the best time to start therapy is when patients advise that symptoms are troublesome. Regardless of when therapy is initiated, achieving good control of motor symptoms is important for quality of life (QoL), as there is a direct contribution of the motor component of disability (mostly as a consequence of bradykinesia) to poor QoL.[21–23] Despite the emphasis on non-motor symptoms in recent years, a longitudinal study of QoL in PD[24] showed that the greatest contributor was loss of mobility, especially in the period before the onset of falls and dementia. Thus, there are reasons to adequately treat bradykinesia and to establish whether the condition is indeed a form of PD that is responsive to treatment.

At the onset of disease, the management of PD is the management of bradykinesia, and all therapies have a relatively long half-life. Consequently, the motor state is relatively constant and does not vary greatly from day to day, or over the day. At this stage and prior to onset of symptom fluctuations, a single assessment adequately measures improvement in symptoms.

With time, patients notice the re-emergence of tremor or bradykinesia prior to the next dose – 'wearing-off' – and dyskinesia at the time of maximum dopaminergic stimulation.[25–32] The time from commencement of therapy to the onset of fluctuations and dyskinesia is similar[33] and occurs after 4–6 years in 40 % of patients and by 9 years in ~70 %.[33–37] The incidence is higher in younger patients, with 92 % of patients experiencing fluctuations after 5 years of treatment.[38] Once fluctuations have developed, the result of assessment will depend on when the test is performed in relation to consumption of medication, and thus more continuous measures are desirable. Often fluctuations become evident to other observers before they are noticed by the patient, who may fail to report them. Failing to detect early fluctuations may constitute a lost opportunity to stabilise the treatment and to improve outcome. Indeed, randomised trials aimed at evaluating the risk of fluctuations with different treatments (for example, comparing agonists with L-DOPA) may be confounded by the presence of patients whose risk of developing fluctuations is low, or by failure to pinpoint their time of onset. If the development of motor fluctuations could be detected by objective continuous measurement then it is possible to establish whether patients benefit from early deployment of continuous dopamine stimulation.

When fluctuations are firmly established, the aims of therapy are to minimise bradykinesia, including that resulting from fluctuations, and to curtail the complications of excess dopaminergic transmission, which include dyskinesia and the non-motor features associated with increased dopaminergic transmission. Thus the goal of therapeutic management is to maximise 'on' time by reducing wearing-off, while at the same time avoiding excess therapy. When wearing-off first presents, treatment effect is predictable. In time, however, this response becomes increasingly unpredictable so that patients cannot plan their days, and the restriction in what daily activities can be managed is much larger than when activities can be planned to 'good' periods of the day.

Treatment of fluctuations entails adjusting the frequency or size of L-DOPA doses, adding agents that prolong the effect of L-DOPA or addition of longer-acting D2 agonists. Effective treatment of wearing off and fluctuations requires a close adherence to medication schedules, yet poor medication compliance is relatively common in PD[39–42] and worst in young patients with many doses/day or when patients were depressed.[39] Non-adherence has been linked to higher total healthcare costs, despite lower drug costs,[43] and presumably this contributes to the poorer QoL of non-adherent patients.[39] Importantly, managing physicians may be unaware of both the lack of compliance and that the patients are undertreated because of this compliance failure rather than loss of response to medication. Being able to objectively measure motor symptoms in relation to compliant drug intake could remove the problem of knowing if lack of response is lack of drug effect or due to poor compliance.

Dyskinesia can be managed by compromising between reduction in bradykinesia and severity of dyskinesia, addition of amantadine or the addition of advanced therapies (DBS, DuoDopa, apomorphine – see Fox et al. 2011[19] for evidence of benefit). The guidelines for the timing of the introduction of advanced therapies use wording such as 'when best medical therapies fail to adequately control motor symptoms.' This wording reflects the current difficulties in objectively measuring motor control. The decision in terms of 'if or when' to introduce these therapies is important because they are expensive, may pose health risks for the patient and are intrusive. There may also be a window of optimum benefit, especially for DBS,[44] so delaying their introduction may introduce the risk of their implementation while forgoing the time when they would have been more beneficial. Effective measurement of fluctuation would enable clinicians to identify, educate and guide patients towards advanced treatment at the time they most benefit from it. A further consideration is that while dyskinesia itself may not have a major impact on QoL, the frequent attendants of impulsivity, dysphoria and anxiety do. Thus dyskinesia can be a surrogate measure of impaired impulse control and affective non-motor symptoms.[45] Non-motor complications of PD, including those that directly stem from the use of dopaminergic therapy directed at alleviating bradykinesia,[3,46–51] are associated with excess disability, worse QoL, poorer outcomes and caregiver burden.[24] Many studies do not explicitly untangle each component's contribution to reduction in QoL, but instead look at the effects of 'non-motor' features on QoL. However, 'treatment policies capable of reducing or delaying motor fluctuations would be expected to increase QoL and reduce some of the economic burden of PD'[52] by reducing both motor fluctuations and those non-motor symptoms caused by fluctuations.

## The Need for Measurement of Motor States

Today, movement disorder clinicians take careful histories designed to identify wearing off and its timing in relationship to medications and to understand the timing and extent of dyskinesia. There are many reasons why, despite a careful and time-consuming history, their best intentions are thwarted. The retrospective approach depends upon the patient's ability to recognise each of the three states (normal, dyskinesia and bradykinesia). Unfortunately, patients are notoriously poor in understanding the difference between dyskinesia and tremor. There are also problems with recall, which are not just 'forgetfulness', but also that immediacy of the current state dominates a patient's idea

of his or herself. So if bradykinesia is the current problem, they have little recollection that last visit dyskinesia was their major concern, and when asked how the last hour was they are more likely to describe the last 10 minutes. People also assess themselves subjectively – a patient comes to regard a certain level of bradykinesia or dyskinesia as 'normal' and will only comment when they are worse than the perceived normal. This is important to remember, because objective measurements, by contrast, use a population referenced baseline that may or may not be relevant to the individual patient. The subjective assessment is also coloured by the affective state and dysphoria of the falling stage of dyskinesia may lead to overrating of the 'OFF' motor state.[53] If someone asks you how often you were hungry or sleepy in the past month or two you may struggle to recall and report that. It may be a challenge even for healthy subjects to reason objectively when asked about past everyday events, so recalling patterns of motor fluctuations can be far beyond the capacity of PD patients with failing executive function.

If the argument that 'management is difficult without measurement' is accepted, then it will be difficult to manage bradykinesia and dyskinesia without knowing its extent, whether interventions were successful and whether therapies were used as directed. Many European countries subsidise the cost of therapies for treating bradykinesia and managing dyskinesia because they enhance QoL and have a health economic justification. If measurement leads to more effective deployment of these therapies, even in a percentage of cases, then costs of therapy would be reduced and QoL improved by that percentage.

## How to Measure Motor Symptoms

The clinical examination of a patient involves the assessment of abnormal motor function and findings are referenced to the examiners previous experiences, coloured by recent impressions and expressed in words. Rating scales, such as the Unified Parkinson's Disease Rating Scale (UPDRS), standardise the examination and present the findings as a pre-defined Likert scale. While these scales reduce the variability of assessments and produce measures that can be compared statistically over time, intra- and inter-rater variability remains high[54] even with the use of video recordings and training. Other frequently used measures of motor impairment and treatment responses include tests that measure the time to perform a defined movement. For example, the Core Assessment Program for Intracerebral Transplantation (CAPIT) protocol[55] includes the stand-walk-sit test, the timed pronation-supination test, the finger dexterity or finger tap test and the hand/arm movement test, which all register movement time.[55] The typical bradykinetic movement pattern with gradually reduced amplitudes and frequencies in repeated movements is however not assessed in timed tests, and the repertoire of symptoms measured in timed tests is restricted.[56–58] This affects the sensitivity of tests as, for example, the chance of detecting abnormal movement is higher with a compound than with a singular movement.[59] Even so, measuring relatively simple movements can add diagnostic information.[58,60]

All tests that involve the assessment of a predefined movement (passive or active), timed or rated, are in a general sense intermittent and cross-sectional. As discussed, PD is a disorder in which the symptoms frequently fluctuate throughout the day and from day to day. Thus a test at a single point in time may fail to capture the full range of variation. In their review, Maetzler et al.[61] described and listed many examples of motor features of PD that an office or laboratory examination fails to capture. They emphasise the need for measures that are continuous, do not require direct elicitation of data from the patient or user and that approximate the real-world activities of the patient.[61]

Diaries have been used as an attempt to approach continuous measurement but their limitations are well recorded.[62] They are labour intensive and have a low compliance rate, particularly if extended for more than 3 days[63,64] and patients may delay recording until the end of each day (or even the waiting room).[65] Paper diaries have a particularly poor compliance rate with compliance often faked,[65,66] but the use of electronic diaries is mainly confined to clinical trials or where patients are carefully selected on their ability to fill in diaries.[62–64]

Recent advances in motion sensors and information storage and handling make continuous, unobtrusive assessment potentially feasible. Although accelerometers have been available for many years, recent computing and data storage capacity has made it possible to use them outside research. Cheap miniaturised accelerometers have become integrated into many electronic devices, including laptops, tablets, smartphones and watches. Actigraphs have been used in PD to measure gait and stability,[67] to trace the development and progression of motor disability over time[68] and diurnal fluctuations.[69] Importantly, it is possible to use mathematical algorithms to recognise movement patterns that clinically experienced raters recognise as bradykinesia[68,70–72] and dyskinesia.[70,73–75] As it is now possible to handle an amount of data that would only 10 years ago have been completely daunting, accelerometers and gyrometers have the potential to objectively monitor motor symptom variations in PD.

## Conclusion

As reviewed elsewhere,[61] systems for continuous measurement are beginning to emerge. In this discussion, focus has been on measuring motor manifestations, with the justification that measurement can lead to a (therapeutic) decision and thus implies the availability of effective therapies. This is by no means to negate the importance however of measurement as tool for better understanding and describing disease and for discovering therapies. Arguably, useful disease-modifying therapies may have been overlooked simply because the measurement tools were insufficiently sensitive to identify their disease-modifying benefit.[14] Similarly, better measurement of many of the non-motor symptoms leads to better understanding of their relationship to motor symptoms and other features of PD and this is an essential precursor to the development of therapies.

On the question of whether objective measurement would improve treatment outcomes, our conclusion is that there is a clear need for continuous objective measures of dyskinesia and bradykinesia that can detect the appearance and patterns of motor fluctuations. The time resolution of validated disease rating scales is insufficient for this purpose and patient diaries are only reliable in selected trained patients. Affordable devices for motion monitoring using accelerometers are available and are good candidate techniques to achieve this. The influence of objective measurements on therapeutical decision-making, patient and carer QoL and the development of PD complications should be further studied. Objective measurements could have a considerable positive effect on PD related health economy by improving outcomes via increasing the detection of untreated bradykinesia (including when manifest as wearing off), early fluctuations and by improving the selection of patients that benefit most from advanced treatments. Also in the evaluation of individual response to altered treatment objective measuring can confirm that the therapeutic decisions have the intended effect. ■

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