Evaluation of the Parkinson’s KinetiGraph in monitoring and managing Parkinson’s disease

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Pharmacological interventions to improve bradykinesia by improving DA levels and dopaminergic neurotransmission.

Bradykinesia results from impaired striatal dopaminergic neurotransmission in the striatum, which in the case of PD is due to reduced dopamine (DA) levels caused by loss of striatal DA terminals. Almost all current therapies for PD aim at improving bradykinesia by improving DA levels and dopaminergic neurotransmission.

1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder with a prevalence of 1.6% (1601/100,000) [1]. There are ~0.9M people with PD (PwP) in the United States [1] and 1.2M in Europe [2]. As the incidence of PD increases with age [3], the aging Western populations will lead to a rapid rise in the prevalence of PD. The classic features of PD are the motor signs of bradykinesia, tremor, and rigidity, although bradykinesia must be present for diagnosis. Bradykinesia results from impaired striatal dopaminergic neurotransmission in the striatum, which in the case of PD is due to reduced dopamine (DA) levels caused by loss of striatal DA terminals [4–7]. Almost all current therapies for PD aim at improving bradykinesia by improving DA levels and dopaminergic neurotransmission.

Loss of terminals impairs the capacity to synthesize and store DA [4,6,8,9]. Consequently, in early PD when some terminals are still present, the response to levodopa (the most common form of DA replacement) requires several days to peak and takes several days to disappear when levodopa is ceased [10]. However, as DA terminals are progressively lost, the capacity to store DA is further attenuated and the duration of the effect of a single dose of levodopa shortens to 2–3 h, mirroring plasma levels of levodopa [11]. The clinical consequence is the reemergence of bradykinesia prior to the each dose, known as fluctuations and ‘wearing-off’ [8]. Dyskinesia is involuntary movement, which most likely reflects altered postsynaptic signaling caused by frequent fluctuations between high and low levels of striatal DA [12] and, almost invariably, accompanies motor fluctuations [13].

The time to onset of fluctuations, ‘wearing-off,’ and dyskinesia are similar with approximately 40% of patients developing fluctuations and dyskinesia after 4–6 years of disease and 70% after long-term treatment (>9 years) [13]. An even higher incidence of motor fluctuations is seen in younger patients, with 92% of patients experiencing fluctuations after 5 years of treatment [14]. In this stage where fluctuations and dyskinesia dominate the picture advanced therapies (ATs) such as deep brain stimulation (DBS), enteral infusion of levodopa or subcutaneous infusion of apomorphine is indicated. People live with PD for approximately 13 years, but the age of death is similar in all patients; so, duration of disease varies with age of onset [15]. Furthermore, all patients appear to spend the last 4 or so years of disease with cognitive impairment, falls, and neuropsychiatry [15], regardless of the duration of disease. These ‘non-motor features’ of PD also include gait dysfunction, neuropsychiatry, autonomic dysfunction, sleep disorders, mood disorders, and cognition [16]. While they tend to dominate late PD, they are present to a greater or lesser extent in early disease also. Some of these non-motor features of PD respond to the therapies that treat bradykinesia and are made worse by doses that induce dyskinesia. Others are relatively impervious to DA replacement therapy. The key points are

1. There are symptoms responsive to DA replacement therapy. The best recognized is bradykinesia but many non-motor symptoms (e.g. aspects of mood, cognition,
pain, and gait) also respond to DA replacement therapy. These ‘DA responsive’ symptoms are the key targets of therapy.

(2) There are symptoms that are caused by DA replacement therapy, including dyskinesia and a number of non-motor symptoms (e.g. impulsivity, anxiety). Minimizing these ‘DA consequent’ symptoms is a key aim of good management.

(3) PD is a fluctuating disorder, especially in the middle phases. It may fluctuate between bradykinesia (representing DA responsive symptoms) and dyskinesia (representing DA consequent symptoms) over the course of a single dose of levodopa (3 h) and from day to day. The aim of therapy is to reduce DA responsive symptoms while minimizing DA consequent symptoms.

(4) PD has three stages. There is

(a) An initial stage, lasting typically 3-5 years and dominated by motor dysfunction but little variation in clinical state over the course of the day or from day to day.

(b) A middle stage, lasting 4–6 years (but much longer in younger patients) in which there is marked fluctuation in clinical response to oral therapies. Managing fluctuations and dyskinesia, timing the introduction of AT, and minimizing non-motor symptoms are the key therapeutic challenges.

(c) A late stage lasting about 4 years, dominated by cognitive impairment, falls, and neuropsychiatry. DA replacement is still effective for motor symptoms but many of the non-motor symptoms are either unresponsive or made worse by this therapy.

2. An unmet need in managing PD

As the aim of therapies is to treat bradykinesia while minimizing dyskinesia, the treating clinician must be establishing the extent and timing of variations and vary the timing and dose of therapy accordingly. This can be difficult because fluctuations between bradykinesia and dyskinesia can occur several times a day and from day to day. In lieu of any objective measurement, the usual approach is to extract this information by history. However, this suffers from patient recall, variations in clinician skill, subjectivity and compounded by the problem that cognition is impaired to a greater or lesser extent in PD. In routine care, the shortcomings of the history are accepted as part of the vicissitude of clinical practice. At times even hospital admission is required, and in some jurisdictions (e.g. Germany), there is funding to allow for this to happen regularly. For research, diaries were developed to capture fluctuations [17,18] but their many shortcomings are well documented [19]: in particular, they are a subjective representation of clinical states that are more readily recognized by a clinical assessment. Thus, the problem in PD is that an expert clinician can make an assessment of a patient at a point in time but there is difficulty assessing the extent and severity of fluctuation in the condition. By comparison, in other disorders that vary over the day or from day to day (such as diabetes or asthma), objective measurement has introduced objectivity about the timing and severity of symptoms, and importantly, it has brought the opportunity of target ranges that represent adequate or poor control. PD, however, has had no objective measurement of disease variation and no target range separating good from poor control, even though there is evidence that greater bradykinesia and dyskinesia results in decreased quality of life and increased costs (Table 1). If PD were to follow the pattern of other disorders, then the availability of objective measurement would be expected to produce target ranges with resultant scores falling into a ‘controlled’ or ‘uncontrolled’ range. Without objective measurement, there are two major failures in management:

- Some patients are thought to be well controlled but are not. The result is worse quality of life and increased costs (Table 1).
- Some subjects are known to have poor control but the severity is erroneously estimated. This results in over or under treatment with worse dyskinesia or bradykinesia than would be otherwise necessary. A special case is when therapy is introduced: without measurement, it is not possible to know if the dose has been optimally titrated and control achieved.

3. Review of objective measurement in PD using the Parkinson’s Kinetigraph System

3.1. The Parkinson’s Kinetigraph System system

As discussed in previous section, there is a need for objective measurement of the main therapeutic target of PD (bradykinesia) and the main motor side effect of excess dopaminergic transmission (dyskinesia). The Parkinson’s KinetiGraph (PKG) [42] was the first system to have the indication to measure bradykinesia from the US FDA, as well as indications for measuring dyskinesia, tremor, and sleep. It remains the only commercially available system providing continuous, objective, and ambulatory assessment of bradykinesia.

The PKG system consists of a wrist worn logger (the PKG logger), proprietary algorithms to produce bradykinesia, dyskinesia, and tremor scores, and a clinically intuitive presentation of this data in graphical and numerical format (the PKG).

Table 1. Evidence that greater bradykinesia and dyskinesia results in decreased quality of life and increased costs.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinesia</td>
<td>[20–23]</td>
</tr>
<tr>
<td>Reduction in QoL is related to severity</td>
<td>[20, 24–27]</td>
</tr>
<tr>
<td>In early disease</td>
<td>[23, 24, 28–31]</td>
</tr>
<tr>
<td>With motor fluctuations</td>
<td>[34–37]</td>
</tr>
<tr>
<td>Failure to take medications has worse QoL</td>
<td>[38, 39]</td>
</tr>
<tr>
<td>Loss of mobility decreases QoL and</td>
<td></td>
</tr>
<tr>
<td>Is improved in part by dopaminergic therapies</td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>[23, 24, 28–30]</td>
</tr>
<tr>
<td>Dyskinesia affects QoL</td>
<td>See Fox [40]</td>
</tr>
<tr>
<td>Therapies improve dyskinesia</td>
<td>[41]</td>
</tr>
<tr>
<td>DBS improves QoL</td>
<td></td>
</tr>
<tr>
<td>Bradykinesia, dyskinesia and fluctuations cost more</td>
<td>[30–33]</td>
</tr>
</tbody>
</table>

DBS: Deep brain stimulation.
3.2. The PKG logger

The logger is a smart watch that is worn on the most affected wrist (Figure 1). It weighs 26 g (46 g including wrist strap) and contains a rechargeable battery and a 3-axis iMEMS accelerometer (Toshiba microprocessor has an integrated MEMS accelerometer) set to record 12-bit digital measurement of acceleration with a range of ±4 g and sampling rate of 32 samples/s using a digital microcontroller and data storage on flash memory. The logger can record for more than 10 days but in normal configuration, after 6 days of recording, data are uploaded to the cloud for analysis. The logger can be programmed to remind subjects to take their PD medications, by delivering vibration, and can detect whether it is being worn. Consumption of medications is acknowledged by swiping the logger’s smart screen. The logger also has sensors to detect whether the device is being worn. The logger is water resistant and has been designed and approved for easy cleaning and reuse.

3.3. The algorithms

An expert system approach was used to model neurologists’ recognition of bradykinesia and dyskinesia on accelerometry data. Inputs to the expert system included Mean Spectral Power (MSP) within bands of acceleration between 0.2 and 4 Hz, peak acceleration, and the amount of time within these epochs that there was no movement. These inputs received were weighted to model neurologists’ rating of bradykinesia and dyskinesia and to produce a bradykinesia score (BKS) and dyskinesia score (DKS) every 2 min.

The PKG (Figure 2) is the graphical representation of the BKS and DKS collected every 2 min over an extended period (typically 6 days). As the device is worn at night to obtain sleep score, these are presented in the PKG, as well as scores of day time sleepiness and inactivity [43]. Other scores include compliance with the reminders, tremor scores [44], and times when the logger was not worn. Over 6 days of continuous recording, there are 4320 2-min data points. The PKG plots the mean BKS and DKS (with a smoothing function) against time of day (Figure 2A). The time that medications were due and consumed is also shown, making it possible to see if there is dose-related variation in BKS or DKS and how the median value at any time of day compares with a normal subject. There are also plots showing the individual scores every 2 min. Raster plots show the time when tremor or sleep occurred or when the logger was not on the wrist. Finally, numerical scores for percent of the time in tremor or asleep and BKS and DKS scores are presented.

3.4. The business model

The PKG system has been approved or cleared for monitoring PD in jurisdictions covered by CE Mark (EU), TGA (Australia), and the FDA (USA). The system is being used in 17 countries and by more than 200 clinics and to date, over 14,000 PKGs have been performed, most in routine clinical care. These clinics have been provided between 5 and 20 loggers. The logger is ‘lent’ to the patient for 6 days of recording and it is the uploading data to the cloud to produce a PKG that generates a fee. Thus, the principle service model is to charge for the service of producing the PKG (report) and providing it to the clinician.

3.5. Validity and utility as a measure of symptoms of PD

The problem in validating a new system for measuring symptoms of PD is that there is no accepted gold standard for comparison. Indeed, the experienced movement disorder clinician is the closest to a gold standard and rating scales have been developed to quantify and standardize the clinician’s assessment. While scales have high internal consistency and inter-rater reliability [45], they only measure a clinical state at a point in time and fail to capture the variation in the clinical state that occurs across the course of the day, and from day to day. The PKG validation of the PKG in measurement of bradykinesia and dyskinesia was achieved by...
In each of these instances, a positive but at times modest correlation was obtained. This was expected because many of these scales are widely considered as unsatisfactory [19] or else are a measure at a point in time compared with a continuous ongoing measurement over the course of several days. The PKG system also monitors other features of PD, including sleep [43], tremor [44,48], and impulsiveness [49]. In each case, these were correlated with a known ‘gold standard’ (polysomnography, laboratory tremorometry, and QUIP scales) with high sensitivity and selectively.

In many ways, however, the most important validation is the utility: Are outcomes superior using objective measurement than with conventional care? Retrospective analyses of the PKG database [50] showed that adding a PKG to a PD patient’s therapy management might contribute to improve patient PD scores. A prospective study (‘the Victorian Study’) was undertaken of PwP [51] taking at least four doses of levodopa/day but considered by their neurologists to be optimally controlled. A PKG was performed on all of these and more than 80% were outside the target range. The most common reason was that patients were unaware and so could not report significant fluctuations. By far the most common reason for being outside of target was undertreated bradykinesia, but 5% were suitable for AT. Patients outside of target were then treated until their scores were within target. There was a significant improvement, as measured by
clinical scales and the PKG, and the effect size was 7 UPDRS III points (which is larger than most oral therapies). An interim analysis was reported [51] and the full study has been submitted.

4. Alternative measurement systems in PD

‘Wearables’ are topical. The number of news releases expounding their potential impact on health care or impending developments significantly outweighs the number of publications showing actual data or value in clinical care. There are several reasons for this noise. Perhaps the most important is the confusion between (and enthusiasm about) the technology that captures data (the data logger) and the algorithms and systems that convert these data into clinical meaningful information that guides therapy and can operate in a regulated environment. This has in part arisen because companies that manufacture ‘bling’ for the wellness industry wish to create interest and income. However, a clear distinction between personal health (which address behaviors and actions that influence health but are under the control of the individual) and Health care (which relates to clinical decisions made by the health profession requiring regulated products) is required. While both may receive regulatory scrutiny, it is the latter that receives the full panoply of protection afforded by regulatory approval (privacy, validity, and safety). It is also the latter that will have the greatest utility. To our knowledge, there are only two systems approved by the FDA for monitoring symptoms of PD and these are the PKG system and the Kinesia system (http://glneurotech.com/kinesia/). The PKG system is the only one that continuously monitors bradykinesia, the key diagnostic criteria for diagnosis of PD and the main therapeutic target.

The PKG system has CE Mark, TGA, and FDA clearance and can be used in clinical care in jurisdictions covered by these approvals. The PKG system was first approved and used in clinical care in Australia and Northern Europe, some Asian countries, and, more recently, in the United States. The path to full reimbursement is being actively pursued in these countries. Development of evidence of utility is actively being developed so as to support these approaches to payors.

5. Limitations of instrumented measuring systems in PD

All measurement systems have limitations and compromises. PD is a non-motor as well as a motor disorder. Aspects of movement can be used as an indirect measure of some of these non-motor features: for example, sleep can be implied by lack of movement and apathy and cognition are correlated with the level of activity and speed of walking. However, these systems are always indirect measures of these features of the disease and none of the systems have mastered continuous assessment of the autonomic system – such as with continuous measurement of blood pressure to capture orthostatic hypotension. While most of the symptoms including the PKG have developed good measurements of dyskinesia, they are at risk of artifacts from exercise and from tremors with significant energy in the low-frequency range. PD commences as a disorder with distal involvement, but this can affect upper and lower limbs differently and it also affects axial movements. Thus, there is a compromise between limited number of recording devices on only one or two limbs, with substantially higher compliance in wearing and using the system, against a greater number of sensor, which produces a more complete picture but is associated with much lower compliance. Higher levels of instrumentation may be accepted by patients in research and pharmaceutical development but are not readily accepted in routine care.

6. Conclusion

PD is a fluctuating disorder and requires continuous objective assessment of bradykinesia, dyskinesia, and other features of PD (tremor, sleep gait etc.) over several days to capture its natural variability and the variability caused by medications. Because of the nature of the neural disturbance in PD, these objective measurement should be made without the patients attention and while patients undertaking their daily routines. Technologies for objective measurement have become available but most do not provide all these requirements of being (1) continuous, (2) measuring key PD parameters (bradykinesia and dyskinesia), and (3) measuring unobtrusively in naturalistic circumstances. The two main reasons for developing this form of objective measurement are for routine care or for research and or development of therapies. This review has focused on the product that meets these requirements for routine care (Table 2). The direct consequence of having objective measurement for routine care is that it will lead to the development of targets that define optimum control of motor systems. These are likely lead to substantial changes in the way PD is managed and to improvements in the quality of life of PwP. Further studies will define and validate these targets and assess the value of optimizing control of symptomatology.

7. Expert commentary

At a conceptual level, an objective measurement for PD would be used to assist a clinician in making an assessment of the severity of the bradykinesia as a representative of DA deficiency in the striatum and aiding in the decision to treat according to whether the symptoms were controlled or uncontrolled (analog to a target for say blood glucose or blood pressure). If a decision was made to treat, then a follow-up measurement to establish whether treatment was effective in achieving control might follow. While this is of relevance at all stages of disease, it will be of greatest benefit in those with unstable and fluctuating disease, in subjects who have difficulty communicating this and with more complex therapy. What follows is a brief summary of specific clinical questions where objective measurement has specific value in PD.

7.1. The patient with fluctuating features

Objective measurement over the course of several days will be greatest in patients whose symptoms fluctuate over the course of a few hours every day. These patients typically
The onset of fluctuations is difficult to detect [55] as the clinician is still the gold standard and the Victorian study (above) suggests that it is commonly overlooked. This can lead to lost opportunity to treat. Furthermore, there is an emerging body of evidence that DBS early in disease may improve quality of life and motor symptoms [54] but this depends on early detection of fluctuations. Thus, there is a case for objective measurement early in disease to detect the onset of fluctuations.

### 7.3. Clinical trials

The value of objective measurement in clinical trials is self-evident. Variance adds to the size and cost of studies and increases the chance of false-positive and -negative outcomes. Reducing variance by increased accuracy and repeatability should be of value in these studies. Finding appropriate populations for clinical trials is difficult for drug and device companies due to the aforementioned variability within the disease and progressive nature of the disease. Objective measurement may be used for patient stratification, for therapy titration in trials and to reduce variance (and ultimately trial size and costs).

#### 7.4. Early detection of disease

As there are currently no disease-modifying therapies for PD, there is less pressure for early diagnosis and treatment. However, there is intense research interest in developing disease-modifying agents with a number of candidates currently under study. The ability to detect disease early would be of value to these research and potentially in routine care when these agents are available. The PKG can detect bradykinesia, asymmetry, and tremor at diagnosis with similar accuracy to the clinician, suggesting that future studies may detect people who have early but ‘nonclinical’ bradykinesia.
patients are managed by the non-specialist. It might be expected that the next 5 years of objective measurement in PD will bring therapeutic guidelines as well as targets.

### 8.3. Non-motor data

With the current accelerometry-based data collection, it is now possible to imply information about a number of so-called non-motor aspects of PD such as sleep and walking. However, autonomic functions including temperature, sweating, blood pressure, and gut motility are close to being feasible providing that the data logging capability meets the demand outlined in the previous section.

### 8.4. Population data

As the number of clinics and cases increases, it will be possible to begin to make comparisons between clinics, regions, and countries in terms of proportions of ‘controlled’ and ‘uncontrolled’ PwP. With 14,000 PKGs already done, it is now possible to note that median BKS are lower in some countries than others. While sampling bias may be a factor, it is more likely that a combination of access to medicine and practice paradigms is a readier explanation. Within countries, trend between individual clinics and regions is also beginning to emerge. Whatever the explanation for this variation, the key point here is to note that in time, it should inform discussion between Health providers, governments, and clinicians as to how best to provide a clinical service to PwP.

#### 9. Technologies for objective assessment of PD

There are many motor and non-motor symptoms in PD. The form and requirement of objective measurement will depend on which of these are being measured and the reason for that measurement. These have been well reviewed elsewhere [56]. We have focused here on objective measurement in the therapeutic management of PD. The requirements here are that

- Objective assessment of the feature being measured will affect therapeutic decision-making. In particular, this means bradykinesia and dyskinesia.
- The measurement must be continuous over several days. This is because measured symptoms will fluctuate with respect to consumption of therapy, over the day and from day to day. Thus, the measurement must cover sufficient period to allow this variability to be assessed.
- Measurements are not be intrusive or complex. This is because measurements are to be made over several days and at every clinical encounter (if other medical conditions are a guide), and intrusive or complex set up will reduce patient compliance. Requiring the patient to wear even two sensors reduces compliance and to don a complex array of sensors will not be effective in routine care. Ceasing routine activities to perform a set of tasks to capture data is also likely to be met with low patient compliance. Furthermore, there is a good argument that process of consciously performing a task reduces the validity of the measurement of both bradykinesia and dyskinesia.
- The system is commercially available. This is important if the clinician is to use it in routine clinical care.

In summary, a device for measuring symptoms for the therapeutic management of PD must (a) record continuously, (b) not require task performance, (c) have simple instrumentation, and (d) commercially available.

Table 2 provides a list of various technologies in the field assessed accruing to these criteria.

#### Key issues

- Bradykinesia is the key target for PD therapies. Fluctuations in bradykinesia and dyskinesia are frequent in PD after 3–5 years from diagnosis.
- Management of fluctuations in bradykinesia and dyskinesia are difficult without being able to objectively measure them.
- The PKG System provides the only continuous objective measurement for bradykinesia in PD.
- Initial studies indicate a substantial improvement in outcome when objective measurement is used.

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### Declaration of interest

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#### References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

This paper describes various approaches to validating ambulatory measurement of bradykinesia and dyskinesia in PD using accelerometry.
• This paper compares diaries and ambulatory measurement of bradykinesia, dyskinesia, and fluctuations in PD using accelerometry.

• This paper compares ambulatory measurement of sleep in PD using accelerometry with other clinical scales.

• This paper describes the methods for ambulatory measurement of impulse control disorders in PD using accelerometry.


