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Parkinson's Disease Management: Trends and Challenges

Angels Bayés¹ and Timothy J Counihan²

¹Centro Médico Teknon – Grupo Hospitalario Quirón, Parkinson Unit,
Barcelona, Spain

²National University of Galway – NUIG, Galway, Ireland

1.1 Introduction

Parkinson's Disease (PD) is a common neurodegenerative disorder that manifests with motor symptoms (MS) and non-motor symptoms (NMS). These symptoms vary from one patient to another and throughout the course of the disease, affecting patients' quality of life (QoL) progressively. Advanced PD represents a public health problem, given that it leads to the reduction in the capacity for self-care and deterioration of the QoL of those affected and their caregivers. The economic cost, including lost productivity and informal care, is about 20 billion euros in the world today.

Parkinson's Disease treatment is symptomatic and aims to alleviate the symptoms associated with the disease, through the precise adjustment of medication. The most widely used drug, levodopa, is effective usually across the lifespan. However, the onset of motor complications (MCs) a few years after starting treatment (e.g., ON-OFF fluctuations and dyskinesias) detract from its value. Symptomatic control of these complications is difficult and must be often optimized because the obtained improvement after such adjustment is not stable over the long term.

Treatment is primarily addressed to reduce the time that the patient is in the OFF state (i.e., time without medication effects), while avoiding the appearance of MCs and NMS, such as hallucinations or impulse control disorder. Reducing OFF hours is, therefore, one of the main parameters used to evaluate the effectiveness of therapeutic interventions, both in medical practice and in clinical trials. Gathering accurate information about the patient's

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condition throughout the day is essential in order to determine the optimal treatment plan. In clinical practice, the only method available is based on diaries filled in by patients and their caregivers about the ON/OFF hours and dyskinesias. However, this method has certain limitations that make unreliable medium and long-term monitoring: motor difficulties, memory failures that hinder regular compliance and subjective evaluation. Therefore, solutions that can improve disease management are of great interest and occupy important part of current research.

Another important aspect of the symptomatic treatment of PD is the multidisciplinary treatment (MDT). The multiple impairments occurring in PD have diverse functional and psychosocial consequences. While the primary treatment is pharmacological, many symptoms do not respond to medication, such as on-period freezing and postural instability. Indeed, later stage disease may be dominated by such symptoms. In addition, there is growing evidence for the efficacy of rehabilitation therapies for specific symptoms, through the involvement of the multidisciplinary team. There is also emerging evidence for physiotherapy with external cueing for improving gait and balance; cognitive movement strategies; and strength and balance exercises. Intensive speech therapy [e.g., Lee Silverman Voice Treatment (LSVT)] has been shown to improve the loudness and intelligibility of speech in PD. Unfortunately, the MDT is only applied in a small number of PD patients for economical and logistic reasons.

1.2 Impact and Strategies of PD at Different Stages

Parkinson's Disease is one of the chronic disorders with the most impact on patients' lifestyle. Most patients survive many years after the first symptoms. The mean survival rate of patients with this disease (when diagnosed after age 50) is 26 years, not very different from the non-affected population.

This disease responds very well to treatment with levodopa and dopaminergic agonists during the first years (between 3 and 7 years). As the disease progresses, the patient encounters a limitation of the effect of medical treatment due to the appearance of motor and non-motor complications. These entail a progressive difficulty in carrying out activities of daily living and leading an independent life. During the first year, the doctor establishes the possible diagnosis and starts one treatment. In course of 2–4 years, there is a relative normality and the medication is generally effective. Between the years 5 and 9, the effectiveness of medication usually decreases and treatment may need to be modified. Problems with driving, finances, and work may appear

Table 1.1 Modified Hoehn and Yahr scale

Scale	Description
1.0	Unilateral involvement only
1.5	Unilateral and axial involvement
2.0	Bilateral involvement without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3.0	Mild to moderate bilateral disease; some postural instability; physically independent
4.0	Severe disability; still able to walk or stand unassisted
5.0	Wheelchair bound or bed ridden unless aided

at this time. During years 10–13, there is an increasing disability: 60–75% of patients present some intellectual deficit, worsening immobility, incontinence, and increased risk of falling.

We can distinguish five evolutionary stages of the disease, although patients may not go through all of them. These are the stages of Hoehn and Yahr (Table 1.1).

The main problems presented by patients in the different evolutionary phases and the strategies currently recommended are explained in the following subsections.

1.2.1 Patients in Early Stages

In stage 1 of PD, facial expression is generally normal and also the posture. Tremor of a limb is the most common initial manifestation. It is often quite annoying, and it is the symptom that draws the attention of both the doctor and the patient. Tremor rarely interferes with the activities of daily living (ADL), although it disturbs and distresses the patient. Patients sometimes report difficulties in performing activities such as buttoning, typing, or cutting food. In the careful exploration of these patients, other parkinsonian signs in a limb, such as bradykinesia or slow movement, and stiffness, which contribute to these fine motor difficulties, are detected in addition to tremor. Decreased arm swing or dragging of a leg when walking can also be observed. These symptoms, often present for several years, are better tolerated than tremor.

In Stage 2 of PD, the involvement is bilateral. There may be loss of facial expression with decreased blinking. Slight flexion of the body may be present and, in general, arm swing when walking is diminished, without altering balance. Patients slow down when performing ADLs, and they require more time to dress, clean themselves up, get up from a chair, or tie their shoes on their own.

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Depressive symptoms are also frequent, and these are detected in between 30–50% of the cases. Medical treatment, which is administered according to the severity of the symptoms, often produces side effects.

In these initial stages, patients are advised to learn about the disease, learn to speak naturally about their problems, learn to share difficulties, and go to the doctor accompanied by someone. Standardized psychoeducational programs, such as the “Edupark” program [1], are of great help during this transition. From the diagnosis, it is recommended to initiate MDT, which includes physical exercise and cognitive stimulation. It is better for patients to continue doing things by themselves, even if it is slowly, without rushing and with enough time. It is advisable to adapt the setting in which patients have to perform their ADLs and to be physically and mentally as active as possible.

Family members should also be informed and should know how to convey their support. It is recommended to see a doctor if depressive symptoms or side effects occur with medications.

1.2.2 Moderately Affected Patients

People with PD in stages 3 and 4 already have a degree of moderate–severe disability, as they experience difficulty walking and with balance. They explain that their gait is shortened, and that sometimes they have difficulties to make turns while they walk, in the corners of the rooms, or to cross doorways. Balance problems can cause falls. Sometimes while walking, they develop freezing of gait (FOG), or difficulty to stand, either forward, propulsion, or backward, retropulsion. The feeling of fatigue is a very frequent symptom. They have the feeling of needing a lot more effort to perform certain tasks, and often notice pains in the cervical, lumbar, or shoulder region. Symptoms of autonomic dysfunction may also be present in the form of orthostatic hypotension, extreme sensations of heat or cold, sweating not related to physical activity, sometimes in the form of crisis, and urinary or sexual dysfunction.

Many patients, at stage 3 or 4, experience side effects to chronic dopaminergic medication. The most annoying side effect for patients is the ON–OFF phenomenon. This phenomenon is often disabling and causes fear and insecurity. During the ON phase, patients can enjoy good mobility and carry out activities outside the home, such as shopping or social activities. However, during the OFF phase the patient may be completely disabled, with difficulty walking, getting up from a chair, or manipulating objects with hands. The appearance of OFF phases limits the social activities of the patient, often preventing them from going out. In this state, patients may find themselves in

really dangerous situations, such as if this phenomenon occurs when crossing a street.

Dyskinesia, or involuntary movements, are another important problem that many patients present with during stages 3 and 4. In general, they have a choreiform nature: creeping movements of the extremities, or masticatory movements of the lower jaw, protrusion of the tongue, oscillations as they walk, and head and neck movements. Dyskinesias are a secondary symptom of dopaminergic medication, which usually occurs during the levodopa peak dose. If they are mild, the family is more aware of these movements than the patients themselves, who usually associate it with free time of parkinsonian symptoms. When they are severe, they can become incapacitating as much as the symptoms themselves.

Non-motor symptoms may appear in the form of sleep disturbances, vivid dreams, and nocturnal vocalizations. Night-time vocalizations, reported by the bed partner, consist of loud cries during sleep often accompanied by agitation of arms and legs. It is called “Rapid eye movement (REM) behaviour disorder”. These events can disrupt sleep. Other frequent behavioural disorders in these stages are visual hallucinations, delusional ideas and confusional states of the paranoid type. Visual hallucinations in general are not very threatening in PD. They often describe the vision of family members, animals, or shadows that become animated objects.

The strategies recommended in these phases are aimed at understanding the MC’s and NMC’s and know how to monitor them. This will allow the patient to adjust the activities in each period. In case of ON-OFF fluctuations, dyskinesias, clinical worsening or behavioural disorders appear, the patient may inform the neurologist who will consider the possibility of a drug adjustment. It is, therefore, important to learn to do the patient’s diary. This information will be crucial to optimize pharmacological treatment.

Patients, in these phases, should continue to maintain an active life and perform MDT, such as physical exercise, occupational therapy, speech therapy, and cognitive stimulation, according to individual needs. It is also recommended to the patient to continue doing things by himself, as long as possible.

1.2.3 Severely Affected Patients

Patients with PD, stage 5, are severely affected. They are usually confined to a wheelchair or in bed and require great assistance to make transfers. They are totally dependent for the realization of ADLs and have a great limitation on a personal level. Difficulties in speech and voice are often accentuated: these patients are often difficult to understand due to their low volume and poor

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articulation of words. They may eventually develop contractures and present decubitus ulcers or recurrent urinary tract infections.

Since the emergence of effective therapies for the cure of this disease, not all patients reach a state of total dependence. However, they are experiencing a progressive reduction in ON time and an increase in dependency time. In the final stages of this disease, the presence of progressive dysphagia can cause recurrent aspiration pneumonia, which is a possible cause of death. Other conditions that may contribute to this outcome are infections of pressure ulcers or urinary tract.

Since a causal treatment of the disease is still not possible, the objective for an optimal treatment will be to obtain for the patient a good QoL and the maximum of independence possible. In the advanced stages, it is recommended to increase the hygiene, to take care of the mobilization, to adapt the feeding and above all to take care of communication. The LSVT method has demonstrated efficacy in the treatment of speech and speech disorders. However, in very severe situations, it is advisable to maintain communication, even if external technical support is necessary.

Possible conduct disorders should be addressed, while enhancing the hobbies and pleasures that can still take place, such as listening to music, reading, or watching movies.

Caregivers should make them feel their support, while they should seek a replacement that allows them to have their own space and thus, avoid the burden of care and better adaptation when the patient passes away.

1.3 QoL in PD

Quality of life means well-being or satisfaction with aspects of life that are important to the person according to social standards and personal judgments. Because of this latter characteristic (i.e., personal judgment), the QoL is understood differently by each person and, therefore, it is difficult to define. The World Health Organization (WHO) defines it as: “an individual perception of the position in a person’s life, in the context of the culture and value system in which he lives, in relation to his goals, expectations, standards and concerns”.

Quality of Life, as related to Health (QoLRH), is the self-perception and assessment of the impact that the disease has on a patient’s life and what its consequences are [2]. This assessment is extremely important because, when it is not possible to cure, maintaining the QoL of the patient is a priority of medical care. Among the different components of QoLRH, main attention must be paid on:

- physical aspects, which are related to symptoms and are functional (i.e., ability to perform activities);
- mental aspects in relation to mood and cognition;
- social aspects such as family role or social relations; and
- economic aspects.

In a recent study by Winter et al. [3], a baseline and 3, 6 and 12 months' assessments were performed on 145 Parkinson's patients. The average annual cost was calculated at 20.095 € per patient. The direct costs involved an expenditure of 13.185 € on medication, 3.526 € on hospital care, and 3.789 € on residences. The indirect costs accounted for 34.5% of the total costs (6.937 €). The costs of home care for the family accounted for 20% of direct costs. Factors associated with a higher total cost were fluctuations, dyskinesias, and younger age.

To assess QoLRH in PD, 56 studies were reviewed [4]. The three most important factors determining QoLRH in PD were depression, stage of the disease, and the time that has elapsed since the onset of the disease.

In another study by Sławek et al. [5], performed with 100 patients, the most important predictor for poor QoL was depression, followed by motor complications. Motor complications, especially nocturnal akinesia and dyskinesia, significantly decrease the QoL of Parkinson's patients [6]. Not only can dyskinesias affect QoL, but they can also increase health costs in patients with PD. This should be taken into account when planning treatment [7].

Despite the high impact of motor symptoms in Parkinson's, non-motor symptoms seem to influence patients' QoL even more [8]. Non-motor symptoms tend to accumulate. The average was 10 symptoms per patient in the populations studied and symptoms tend to intensify over time. Depression, anxiety, fatigue, sleep disorders, pain, orthostatic hypotension, and profuse sweating are some of those that have shown an individual relationship with loss of QoL. In fact, any symptom that, due to its intensity, is installed as a central problem in the life of the patient has a direct and important impact on his or her QoL. For example: difficulty swallowing, persistent constipation, urinary urgency and night-time urination, delusions and hallucinations, memory problems, or a sense of choking when breathing. At the global level, the main factors influencing the poor QoL of those affected by PD are (in order):

1. Depression
2. Overall disease severity (Hoehn and Yahr stage)
3. Dyskinesia

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4. ON–OFF fluctuations
5. Age
6. Insomnia
7. Tremor
8. Cognitive dysfunction

Another element that must be taken into account is the QoL in caregivers of patients with PD [9]. 40% of caregivers indicate that their health suffers from caring. Nearly half have increased depression, two-thirds report that their social life has suffered. The caregiver becomes burned out more (burden of care) if the patient has more disability, or affective problems, mental confusion, or falls. There is a correlation between those caregivers that are most affected and the degree of a patient's depression. The conclusion is that more attention should be given to caregivers' care, particularly in advanced stages and/or with psychiatric and fall complications. These findings demonstrate that the QoL of both the patient and the caregiver depends, to a great extent, on the inclusion of the burden of care as one of the problems associated with PD [10].

1.4 State of Art of Current Trends in PD Management

The current treatment of PD is symptomatic and is applied through pharmacological and/or surgical treatment, associated with MDT.

The pharmacological treatment of PD aims to alleviate the symptoms associated with the disease, through the precise adjustment of medication. During the first few years of treatment, dopaminergic drugs are usually very effective. When the ON–OFF phenomena are already present, this objective is reached essentially by reducing the time during which the patient is in the OFF state, while avoiding the appearance of MCs and NMS. The reduction of OFF time is, therefore, one of the main parameters used to evaluate the effectiveness of therapeutic interventions, both in medical practice and in clinical trials. To determine the optimal treatment plan, gathering accurate information about a patient's condition throughout the day is essential. In clinical practice, the method currently available is based on diaries filled in by patients and their caregivers, recording hours of ON–OFF and the presence of dyskinesia. However, this method has limitations that make it unreliable, such as motor difficulties, failures in memory and in compliance, and subjective evaluation. It is necessary to know precisely the effect of drugs on reducing OFF hours and increasing the ON hours in Parkinson's patients. Reliable tools are, therefore, needed for detecting the motor condition of patients.

In patients with advanced PD, in which it is very difficult to control MCs and NMS through pharmacological adjustment, interventional therapy strategies are increasingly applied. These treatment strategies are aimed at obtaining continuous dopaminergic stimulation (CDS), either by using an infusion pump to deliver medication or by deep brain stimulation (DBS). However, these techniques are expensive, and often difficult to manage by the patient. Well-designed clinical studies on these interventional therapeutic approaches provided evidence for the efficacy of DBS and CDS in advanced PD and opened new perspectives for their use in earlier disease stages also.

On the other hand, there is growing scientific evidence of the benefit of the application of MDT, such as physiotherapy, speech therapy (e.g., LSVT), occupational therapy, cognitive stimulation, and psychoeducation in the treatment of Parkinson's Disease. Intensive and multidisciplinary rehabilitation slows the progression of motor decay, and slows the need to increase treatment with levodopa, which is postulated to have a neuroprotective effect [11]. Therefore, the application of MDT from the moment of diagnosis seems of great interest. There are several studies of multidisciplinary care in PD comparing outcomes before and after the intervention. Outpatient multidisciplinary care programs have reported short-term improvements in UPDRS (Unified Parkinson Disease Rating Scale) motor score, gait speed and stride length, speech, depression and health-related QoLRH. Long-term improvements in motor function have also been reported, and the authors comment that a close collaboration among members of the multidisciplinary team was essential to obtain the best results.

Potential limitations to the implementation of effective MDT are: distance, insufficient expertise among health professionals, poor interdisciplinary collaboration, poor communication, and lack of financial support for a multidisciplinary team approach. Regular face-to-face team meetings are important for effective functioning of the team. These meetings allow sharing of pertinent information and ensure the team is working towards shared goals for any given patient. The meetings can be a forum and stimulus for staff education, driving up quality of care. This type of coordinated multidisciplinary approach is sometimes referred to as interdisciplinary.

Most hospitals in Europe do not have a multidisciplinary service for the care of people with PD. These types of therapies are expensive and in addition, their application requires patients to frequently go from one place to another. This entails a number of limitations, both economic and logistical, for those affected with PD before having access to these therapies.

1.5 Needs and Challenges for Optimal PD Management

Current management of advanced PD is complicated and problems arising from poor QoL affect many patients. In 2001, *the Committee on Quality of Health Care in America Institute of Medicine* provided an objective analysis on healthcare. The report listed six aims, proposing that health care should be: safe, effective, patient-centred, timely, efficient, and equitable. However, current care for PD in the US, Europe, and likely the majority of the world, frequently does not meet these six aims [12]. PD care is often not safe. Individuals with PD who are hospitalized are often subjected to delayed treatment, contraindicated medications, prolonged immobility, lengthy stays, and high mortality [13, 14]. There are some comprehensive and distributed PD care models that are quite effective, but only few patients receive such care. Many PD-related hospitalizations are likely preventable. The patient-centred care that is timely has been rarely studied. Despite the limited evidence, focus groups and surveys suggest that individuals with PD want more personalized information from multiple disciplines that is delivered remotely in a timely manner [15]. PD care is very inefficient. Patients and their caregivers spend hours travelling and waiting in the clinic for routine follow-up appointments or for the application of complementary therapies.

Finally, and perhaps what may be most concerning, there exists inequity of current PD care. A primary determinant of the care that will be received is where you live. In the US, 42% of individuals with PD older than 65 and up to 100% of individuals in some rural areas do not see a neurologist soon after diagnosis [16]. In Europe, the first right expressed in the European Parkinson's Disease Association Charter is care from a physician with a special interest in PD. However, 44% of Europeans do not see a PD specialist in the first 2 years after diagnosis. Beyond neurological care, access to specialist nurses, occupational therapists, and counsellors is often more limited [17]. In less wealthy countries, the situation is even worse. China only has approximately 50 movement disorder specialists to care for more than 2 million individuals with PD and Bolivia only has 15. A door-to-door epidemiology study found that none of the individuals identified with PD had ever seen a physician, much less received treatment.

We can make the treatment safer, effective, patient-centred, efficient, and equitable only with the application of two conditions: that the treatment is applied mostly in the patient's home and with the use of tools, based on new technologies: sensors, communication platforms, and smartphones. This will overcome economic barriers and physical distance.

The simple fact of detecting accurately and reliably the clinical condition of the patient can mean a significant advance in the QoL of the patient, as this will affect a much more accurate adjustment of medication. In addition, with the help of adequate platforms, many more patients, as well as their caregivers, will receive more specialized medical care, complementary therapies, and psychoeducation as often as necessary, regardless of where they live.

In addition, reliable detection of the motor status of PD patients throughout the day can drastically change the value of drug clinical trials. Finally, the careful selection of patients amenable to the semi-invasive therapy options becomes more and more important and should be timely. An interdisciplinary setting is required to account for optimal patient information and awareness, selection of best individual treatment modality, training of relatives and caregivers, management of complications, and follow-up care.

The application of this type of tool is also of great interest in this section [18].

From a clinical point of view, the development of new technologies in the management of Parkinson's Disease must be validated so that the improvement of the QoL related to health is the main objective. Symptom-monitoring tools should be based on these premises: to provide a valid and accurate parameter of a clinically relevant characteristic of the disease; to find evidence that the parameter has an ecologically relevant effect on the specific clinical application; that a target interval can be defined in which the parameter reflects the appropriate treatment response; and finally, that the implementation is simple to allow repetitive use [19].

Remote monitoring from devices, such as wearable sensors, smartphones, platforms, disease management applications, smart beds, wall-mounted cameras, smart glasses, and even utensils, can monitor a patient's symptoms and function objectively in their environment, facilitating the delivery of highly personalized care.

Another aspect to improve PD care is that the most of it must be delivered at home. Current care models frequently require older individuals with impaired mobility, cognition, and driving ability to be driven by overburdened caregivers to large, complex urban medical centres. Moving care to the patient's home would make PD care more patient-centred. Demographic factors, including aging populations, and social factors, such as the splintering of the extended family, will increase the need for home-based care. Technological advances, especially the ability to assess and deliver care remotely, will enable the transition of care back to the home. However, despite its promise, this next generation of home-based care will have to overcome barriers, including

outdated insurance models and a technological divide. Once these barriers are addressed, home-based care will increase access to high-quality care for the growing number of individuals with PD.

Emerging care models will combine remote monitoring, self-monitoring, and multidisciplinary care to enable the provision of patient-centred care at home and decrease the need for in-clinic assessments.

The demand for in-home care is likely to grow as a result of demographic, economic, social, and technological factors. Both the absolute number and proportion of older individuals with PD will increase.

1.6 Conclusion

A system for PD management will be necessary in the near future. It must be able to reliably assess the symptoms, facilitate patient disease management, and give them independence and the best QoL. At the same time, the tools must help the patient to stay physically and mentally active as much as possible. Finally, they must provide the neurologist with disease management tools to optimize the treatment.

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