Universidade de Lisboa

Faculdade de Farmácia

Análise Preditiva de Dados em Cuidados de Saúde

Otimização de resultados pela monitorização da progressão da doença

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Monografia orientada pelo Professor. Rui Miguel Dias Loureiro,
Categoria Professor Auxiliar Convidado

Mestrado Integrado em Ciências Farmacêuticas

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Resumo

O aumento do custo de vida, o envelhecimento da população e a prevalência de doenças crónicas estão a mudar a saúde tal como a conhecemos hoje. Para responder a estas mudanças, o sector da saúde tem vindo a sofrer várias transformações, quer ao nível de novos processos, quer ao nível da implementação de novos sistemas e softwares. A revolução digital trouxe uma necessidade acrescida ao nível da gestão e análise dos dados deste setor, uma vez que o foco está agora centrado no doente. O principal objetivo desta análise é melhorar os cuidados prestados, quer em termos de qualidade, eficiência e mesmo de custo. Desde a existência de uma maior evidência clínica para apoiar a tomada de decisões, rapidez na identificação de doenças de alto risco, emissão de alertas em tempo real para os profissionais de saúde, tudo isto permite uma assistência médica rápida e eficaz, bem como cuidados pessoais e informais.

Em particular, a doença de Parkinson é extremamente complexa e heterogénea, dado que cada doente tem um ritmo de progressão e uma combinação de sintomas totalmente diferentes, levando assim à existência de muitas lacunas na sua compreensão, tanto a nível científico como na prática médica. Assim, a única forma de resolver estas carências e chegar a conclusões cientificamente corretas é recolher dados sobre os sinais e sintomas, mais especificamente da sua intensidade e progressão.

De modo a responder a esta necessidade, neste trabalho realizamos uma revisão da literatura e propomos o desenvolvimento de um software cujas funcionalidades permitem a monitorização dos sintomas destes doentes. Através da aplicação proposta, será possível recolher dados de diversos patientes, e monitorizar a doença com vista a retardar a sua progressão. Depois disto, e como aplicação direta desta recolha, devemos trabalhar no desenvolvimento de um algoritmo que através da monitorização dos sintomas auxilia a gestão do tratamento, para qualquer doente. Este software deve sempre ter em conta as particularidades de cada doente, sobretudo a sua idade, comorbilidades, duração e intensidade dos sintomas, causa dos sintomas, e medicação concomitante.

Palavras-Chave: Doença de Parkinson, sintomas, gestão da doença, monitorização dos sintomas, aplicação móvel

Abstract

The rising cost of living, an aging population and the prevalence of chronic diseases is changing health as we know today. To respond to these changes, the health sector has been undergoing several transformations, both in terms of new processes and the implementation of new systems and softwares. The digital revolution has brought an increased need for the correct management and analysis of data from this sector since the focus is now centered on the patient. The main goal of this analysis is to improve the care provided, both in terms of quality, efficiency, and cost. From the existence of greater clinical evidence to support decision-making, speed of identification of high-risk diseases, delivery of real-time alerts to health professionals, all this then allows for fast and effective medical assistance, self, and informal care.

In particular, Parkinson's disease is extremely complex and heterogeneous, since each patient has a different rate of progression and combination of symptoms, thus leading to many gaps in its understanding, both scientifically and in medical practice. Therefore, the only way to address these gaps and reach scientifically correct conclusions is to collect data on the signs and symptoms, in particular their intensity and progression.

To meet this need, in this study, we conducted a literature review and proposed the development of a software application whose functionalities allow the monitoring of these patients' symptoms. Through the proposed software, it will be possible to collect data from several patients and monitor the disease with the intent of slowing its progression. After this, and as a direct application of the gathering of this information, we should work on the development of an algorithm that, through symptom monitoring, helps manage treatment for any patient. Such software should always consider each patient particularities, especially in terms of age, comorbidities, duration, and intensity of symptoms, cause of symptoms, and concomitant medication.

Keywords: Parkinson’s Disease, symptoms, disease management, monitoring of the symptoms, mobile applications

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1. Introduction

Parkinson's disease is currently the second most prevalent neurological disorder, having shown an exponential increase in recent years. This disease is extremely complex and heterogeneous, so in addition to the cardinal symptoms that characterize it, particularly tremors, postural instability, and muscle stiffness, it also presents several highly unspecific symptoms. (1)

For this reason and given the lack of means of detection that allow the correct diagnosis of the disease, it is extremely important to analyze all the symptoms and particularities of the patient, to exclude parkinsonism's. Therefore, it is crucial to analyze each patient individually. (2–4)

The use of an application software can be a solution to this problem since it allows the gathering of a vast amount of information over time. This, in turn, can help the medical team to select the most appropriate treatment for each patient. (5)

In this paper, we propose to perform a systematic review of the existing literature about this disease and of the existing applications that allow monitoring of these symptoms. However, we verified that there is no complete and integrative application that can monitor and collect this kind of data.

As such, one of the goals of this work is to propose the development of a software that monitors all the symptoms of the disease, collects this data, and supports both the patient and the caregiver in living with the disease and the impact it may have.

Additionally, one advantage of gathering this data regarding the progression of different symptoms is the standardization of its content for the development of an algorithm that facilitates decision-making by clinicians, considering the symptoms presented by these patients. However, for these data to be valid and meaningful, they must follow certain standards, be objective, and collected over a substantial period in order to later be evaluated and analyzed appropriately.

2. Predictive Analytics

2.1. Definition

The ability to predict events occurs more and more these days, from weather forecasting to the development of mathematical algorithms. We use collected historical data to make predictions about future events - this data allows us to identify patterns and trends, calculate potential scenarios, and make strategic decisions based on those forecasts. These can be made in the short or long term, and allow us to analyze risks and opportunities, and the comparative effectiveness, for example, of different drugs or treatments. (6)

Through these models, predictive analytics helps healthcare organizations to improve patient care and thereby improve patient outcomes. While there is a growing literature on predictive data in healthcare, specifically using Artificial Intelligence (AI), we only have significant analysis and research on a few diseases, namely cancer, cardiovascular accidents, and nervous system diseases. (7)

There are two essential features to any successful predictive analytics application - a structured data component, where images or videos are inserted, and an unstructured data component, such as log files. Companies are overloaded with data, such as electronic records, administrative data, clinical trial data, data from mobile apps and devices, or even social networks, and it is this data that will serve as the baseline for these algorithms. Afterwards, this data undergoes statistical modeling to adapt this information through innovative data mining and machine learning techniques. This customization and standardization allow the data to achieve its purpose, that is, to make a diagnosis or manage a treatment for different patients with unique characteristics using one single tool. (8)

2.2. Advantages

The progress in terms of health databases, big data platforms, and artificial intelligence, if used correctly, will potentially allow to (I) predict and prevent situations considered critical before the need for emergency care, thus reducing the number of patients readmitted to the hospital, (II) optimize the number of professionals, reducing waiting times and improving the speed of care, (III) personalize the treatment for each patient as the diagnosis is determined for that specific individual, which improves the care provided and consequently the outcomes obtained, and finally, (IV) by optimizing all these resources, we end up reducing the money spent on healthcare. (9)

Many entities, particularly insurance companies, invest in the acquisition of predictive analytics algorithms to obtain information that helps improve the quality of care, reduce waste throughout the system, which ultimately reduces the costs associated with the supply of care, and improves customer satisfaction. In other companies, this predictive analytics is an essential tool for decision-making, as it forecasts sales, which allows production to be optimized, and these resource savings can be invested in the development of new products. (10)

2.3. Limitations

Despite having countless strengths, predictive analytics also has some disadvantages. The main limitation is the lack of legislation, as there are no standards that evaluate the safety and effectiveness of these AI algorithms. For this reason, the FDA decided to share some guidelines to help overcome this difficulty, which led to the development of the first clinical learning platform for cardiovascular diseases. (2)

Another challenge is how to standardize this data. No matter how sophisticated they are, they must be reviewed and "trained" to fit the health data, and to serve as support for decision making on a diagnosis and/or treatment.

A very controversial topic these days, and certainly one of the biggest challenges facing all analysts, is how to manage data with respect to patient privacy. Although there are laws regarding the protection of this data, they are often shared with healthcare companies to be used for the predictions stated above. (11)

There is still no consensus about the possible replacement of doctors with Artificial Intelligence. AI has been seen as an enormous potential to support clinical decision-making, however, there is concern about what biases may be associated with the algorithms developed, and what consequences they hold for health inequality. These systems are already being trained to analyze medical tests and samples to reach a diagnosis. One of the most studied areas has been breast cancer. (12) For the time being, it is believed that these technologies will serve as a complement to medical expertise rather than a replacement, but in the future, this may change. The integration of these systems is still very recent since there is a lack of data, and without it, it is not possible to "train" this software to know how to read them and reach a decision. (13)

3. Parkinson Disease

3.1.What is Parkinson's Disease?

In 1817, the first description of patients with Parkinson's Disease was written and published by the English physician James Parkinson, under the title "An Essay on the Shaking Palsy". The decrease and slowness associated with the movements of Parkinson's disease patients were initially interpreted as weakness, hence the name given by Parkinson to his work. Only later it was assumed to be an inability to produce a normal level of strength. (14)

This first official medical paper described the symptoms inherent to the disease that a doctor might observe in his patients, particularly postural instability, and tremors in several parts of the body, such as the hands and arms. It is interesting to note that the diagnostic criteria mentioned in this document have remained practically unchanged to this very day. (15)

Parkinson's disease (PD) is a progressive neurodegenerative condition that affects the nervous system and the parts of the body controlled by the nerves. The main difference between PD and other movement disorders is that cell loss and/or insufficient cell production occurs only in a specific region of the brain, called substantia nigra pars compacta (SNpc). When the dopaminergic neurons of the substantia nigra die or become insufficient, they lose the abilities those areas once controlled. This causes a decreased production of dopamine - the neurotransmitter associated with the regulation of movement. As a result, the brain does not have enough dopamine to send activation signals that tell the muscles to move, resulting in movement-related problems that are characteristic of this disease. These include bradykinesia, tremor, stiffness, and, later, postural instability. (16)

The reason why these neurons die is still being studied. Some of the risk factors possibly associated with it include aging, family history, exposure to pesticides or environmental chemicals. However, its ultimate cause remains unknown. (17)

For much of history, Parkinson's Disease was considered a rare condition. After this disorder had first been described, there was an increase in awareness around the symptoms, and less than two centuries later, this rare condition has become a quite common disease around the world. (10) The proof that this disease is relatively unknown in terms of genetic studies, is that the first GWAS (Genome-Wide Association Studies) loci, was only identified in 2009. Since then, the influence of genetic factors on the disease and its progression have been studied, as these are possible examples of therapeutic targets that can delay or stop disease progression. (18)

3.2. Stages of Parkinson's Disease

In 1967, Margaret Hoehn and Melvin Yahr, created a scale to measure the progression of Parkinson's Disease according to the level of clinical disability. Considering the patient's symptoms and their severity, the physical signs observed by the doctor and patient's functional capacity, they were divided into several stages. Stages 1 and 2 correspond to the early-stage, stages 2 and 3 to the intermediate stage, and stages 4 and 5 to the advanced stage of Parkinson's Disease. (19–21)

Sometimes patients unintentionally ignore the first stage because the symptoms are not so intense. On the other hand, they may never reach the threshold of stage five. So, we see that the scale is not straightforward, with patients progressing between stages at completely different rates, and no stage directly representing a specific pathology in the brain. On the scale, we move from the first stage, where symptoms are milder and the person is independent in his or her daily activities, to the last stage, where symptoms are already felt in a more critical way and patients are conditioned and dependent on the help of a caregiver. (19–21)

Follos a brief description of the different stages of this disease.

I) Stage One – Changes in a Person's Habits

In stage one, the patient has mild symptoms that have no impact on daily activities and overall quality of life, which is why this stage is often neglected. Nevertheless, symptoms are present and those close to the patient begin noticing changes in their movements, posture, or even facial expressions, however these are so mild that they do not justify a visit to the doctor. The most common symptoms are tremors, stiffness, slowness, and lack of movement, usually affecting one side of the body. Thus, this stage is characterized by unilateral involvement, usually with minimal or no functional incapacity. (19–21)

II) Stage Two – Stiffness and Posture Problems

At this stage of the disease, the patient starts to present symptoms on the opposite side of the body. Here, tremors, muscle stiffness, rigidity and postural instability can make everyday tasks more difficult and time-consuming. However, other symptoms may also appear, such as lack of facial expression and speech abnormalities, associated with monotony or changes in voice volume. The symptoms in this phase may also affect the patient's posture and gait, leading to back and/or neck pain. (19–21)

The main difference from the previous stage, apart from the increased intensity of the symptoms, is that both sides of the body or even the midline (neck or trunk) may be affected. Even so, the symptoms remain more severe on one side. This stage is then characterized by bilateral involvement with the compromise of the patient's balance. (19–21)

III) Stage Three – Poor Reflexes and Balance Issues

In this third phase, the disease presents itself through bilateral involvement, which can be classified as mild or moderate, associated with postural instability. Despite this, patients remain physically independent in all their daily activities, such as eating, cleaning, and dressing. Loss of balance is then the main hallmark of this stage of the disease. The patient loses the ability to react quickly and to protect himself from falling, which becomes one of the most dangerous and challenging aspects to correct. It is from this stage onwards that falls become more frequent and the symptoms more intense. (19–21)

IV) Stage Four – Poor Motor Skills

The main difference between stage three and stage four is independence in performing tasks. Patients in this stage can no longer lead an independent life, needing help, either from a caregiver or an assistive device, due to the fact that they have significant limitations in terms of movement and reaction time. For this reason, some daily tasks can become difficult or even impossible. This stage is then characterized by significant disability; however, the patient is still able to get up and walk without help. (19–21)

V) Stage Five – Severe Stiffness

This is the last stage in the progression of Parkinson's disease. In this stage, advanced stiffness of the legs is observed, making it impossible to walk or even stand, which is why many patients use wheelchairs or are confined unless they are helped, which means constant assistance. It is also at this stage that greater confusion and possible hallucinations are manifested. (19–21)

The development of dementia at this advanced stage of the disease is very frequent, about 50 to 80% of Parkinson's patients eventually develop this disorder. At this stage, one of the priorities is to evaluate whether the side effects from the medication outweigh the benefits for the patients. (22)

The classification system aforementioned has fallen into disuse, as it was perceived that it is more useful to determine the impact and limitation of the disease on an individual's life and

treat it, than to classify the disease itself. Despite these drawbacks, this classification proved to be practical for many years, since it was a simple method that allowed reproducible assessments of the patient's general condition and functional level by independent examiners. As the definitions of the stages were very precise, confusion due to ill-defined terms such as mild, moderate, or severe disease was avoided. (17)

There are other scales to quantify the severity of Parkinson's Disease: The Unified Parkinson's Disease Rating Scale (UPDRS), the modified Columbia Scale, the Webster Scale, the Schwab and England Disability Scale, the Northwestern University Disability Scale, and several others, each with its own characteristics and usefulness. (23)

According to this new classification system, we have four parameters that may be affected by the disease and that are likely to be observed and evaluated by health professionals, namely the non-motor part associated with daily activities, the motor part associated with those same activities, an observation of motor skills, and the complications that arise from this condition. (23)

I will now present the symptoms most frequently associated with Parkinson's Disease.

3.3. Symptoms

PD is accompanied by motor symptoms, such as slowness of movement, tremors, stiffness, rigidity, and difficulty with balance and coordination; and by non-motor complications, such as cognitive impairments, mental health disorders, sleep problems, pain disorders, obstipation and gastrointestinal problems, apathy, fatigue, and sensory disturbances, among others. Other reported symptoms are depression, difficulty in chewing, swallowing, or even speaking, urinary tract problems, and skin problems. (24)

The symptoms may often appear in only one part of the body, and these initial symptoms may be milder or go unnoticed, but they worsen and increase as the disease progresses. Non-motor symptoms appear a lot during the development disease. However, many of these problems may even precede the diagnosis by several years - such as depression or sleep problems. Thus, these changes may appear before the cardinal motor symptoms and evolve equally in severity and diversity. (24)

a) Resting tremors

Resting tremors is one of the most common symptoms of Parkinson's disease, considered an involuntary, rhythmic, oscillatory movement between the frequencies 4-8 Hz that occurs mainly when the muscles are at rest. (25,26)

There are several possible forms of tremor, and it is important to distinguish between resting tremor and essential tremors during voluntary muscle contraction. The tremor can range from moderate to severe and is extremely sensitive to stress. It can also affect different regions of the body, such as the hands, tongue, arms, the legs, or the chin. When isolated head tremor occurs, which is rare, it should be reported as it may alert to a differential diagnosis of non-degenerative tremors. (25,26)

This symptom is characterized by its high heterogeneity, and complexity of its physiopathology which is totally different from the other cardinal signs. Its origin is still being investigated and contested. Several neurotransmitters are associated with the origin of tremors, such as dopamine, acetylcholine, serotonin, and noradrenaline. These differences in tremors' pathophysiology are important to be researched and developed to further establish a specific biomarker for targeted therapy. (25,26)

b) Slowness and paucity of movement

Bradykinesia, which consists of a progressive decrease in speed, and hypokinesia, characterized by a decrease in the amplitude of movements are among the most common symptoms of PD. It can also be associated with the term akinesia, when the two phenomena of absence of movement and delay in the onset of movement occur. This leads to a decline in the spontaneous body movements and can even end in a complete stop of movements. This symptom is often confused with simple slowness, which can be caused by generalized pain or decreased muscle strength, both of which are common factors to most people at this age. So to avoid misdiagnosis, we must ensure the correct identification of the symptom and its potential causes. That is because the complete assessment of this disease requires the presence of this symptom. (14)

c) Limb stiffness and rigidity

As cardinal signs of Parkinson's Disease we have stiffness and limb rigidity. Without the presence of these symptoms, we cannot make an accurate diagnosis of this pathology. The

mechanisms behind the stiffness are still being studied since there is no consensual response from the scientific community to this problem. (27)

There are several methods used to assess and quantify these symptoms, and all of them have a good correlation and validity with the clinical scales used. Through these methodologies it was possible to confirm the high values of stiffness, both at rest and during the movements, of Parkinson's patients, when compared to healthy people. (27)

d) Impaired posture and balance

Postural instability (PI) and imbalance are the most common symptoms in PD, although they only appear in a late stage of the disease, more specifically from the third stage onwards, according to the scale presented earlier. This PI is due to sensory, visual, and proprioceptive dysfunction, but also to the loss of postural reflexes, which leads to difficulty in maintaining balance and adopting a correct posture. (28)

Studies show the limited effects of existing treatments for this problem. From dopaminergic drug therapy, or even resorting to deep brain stimulation, it is thought that the best approach is non-pharmacological, at the level of rehabilitation, for example, to reduce the number of falls. This risk is associated not only with reduced muscle mass, but also with the postural instability characteristic of these patients, thus increasing from 39% in a healthy elderly person to 68% in a person with PD. Thus, an innovative approach is needed to include moderate exercise, more specifically resistance and balance training, in the routine of these patients to prevent disability and to improve posture and balance control. (29)

Other disorders, also known as dyskinesias and dystonias, cause limitations at multiple levels, including speech and mobility, and usually occur in later stages of the disease. (29)

e) Speech and communication problems

Speech disorders are very common in individuals with Parkinson's disease. Many patients speak softly and in one tone, sometimes sounding breathless or having difficulty pronouncing letters or words, but some have rushed speech, even stuttering. The usual motor symptoms, such as decreased facial expression, dysarthria, and reduced sensory awareness can exacerbate the communication problems. (30–32)

These difficulties arise since Parkinson's affects muscles and nerves in the face, throat, mouth, and the respiratory system, but it also affects the areas of the brain that process information and control the speech process, therefore making it more difficult to engage in conversations. (30–32)

f) Writing changes

Some Parkinson's patients report that as they write, their handwriting becomes smaller, a phenomenon called micrography. The reduced speed of writing and sentence length itself, along with the interruptions and movement changes, are noticeable in the writing of these patients. There are countless factors that can impact writing, including tremors, lack of coordination, muscle stiffness, and difficulty controlling their own movements. To correct this problem, dopaminergic medication should be combined with some strategies to recover writing techniques, since this is a capability that can be worked on or even relearned. (33)

g) Sleeping problems

PD is associated with many sleep disorders that impact the quality of life of these patients. Healthcare professionals must assess the sleep quality of patients to ease the detection of these problems and their clinical management with the other symptoms of PD. (34)

The motor symptoms of PD such as tremors, rigidity, and bradykinesia might contribute to these sleep rhythm disturbances, but the use of dopaminergic drugs can also affect sleepiness levels. (35)

Early insomnia, Excessive Daytime Sleepiness (EDS), obstructive sleep apnea, Restless Legs Syndrome (RLS), circadian rhythm disturbance, frequent nightmares, and confusing awakenings are some of the better-known examples of sleep problems associated with Parkinson’s Disease. (36)

One of the most common problems is restless legs syndrome. It starts or gets worse at night and is characterized by a feeling of discomfort when the legs are stationary, followed by the need to move them. It can also be the cause behind insomnia. Another common condition is excessive daytime sleepiness, which corresponds to the difficulty in staying awake and alert. This condition has a negative impact on patients' lives as it increases the risk of falls. (36)

h) Anosmia and Ageusia

Both anosmia, loss of the sense of smell, and ageusia, loss of the sense of taste, are key features of Parkinson’s Disease, since they are present in most of the patients and impact the quality of these patients. (37) Clinical evidence shows that anosmia is associated with the cognitive impairment typical of Parkinson’s patients. (38)

i) Gastrointestinal Tract problems

Although the diagnosis of this disease is made based on motor symptoms, clinical evidence indicates that gastrointestinal tract problems may be considered early biomarkers since, in most cases, they appear before motor manifestations. (39)

Gastrointestinal tract (GIT) dysfunction affects the quality of life of Parkinson's disease patients and includes symptoms such as abnormal salivation, dysphagia, constipation, abdominal bloating and pain, nausea, vomiting, early satiety, and fecal incontinence. Some of the causes for these disorders are pharyngeal lack of coordination, changes in peristalsis, chronic pain, and alterations in GIT permeability. (40)

Abdominal pain may be a consequence of motor fluctuations, so timing and dose adjustments should alleviate symptoms. However, gastroparesis itself may increase the transit time of drugs to the gut, increasing pause periods. Constipation is probably the most common symptom in this group and occurs due to delayed bowel transit time and decreased motility. This results in difficulties in defecation, which are quite common in these patients and may manifest even before motor symptoms are noticeable. This difficulty is due to a lack of coordination of the defecation muscles, resulting in ineffective elimination of feces. (41)

j) Blinking less often than usual

Decreased blinking is a characteristic symptom of PD and shows reduced control of the facial muscles. The movements are longer and there is a reduced frequency of spontaneous movements such as blinking or even smiling, which gives the appearance of a fixed stare, as if the patient had no expression. (14,42)

k) Trouble swallowing

Almost 80% of Parkinson's patients experience swallowing disorders throughout their disease. Swallowing dysfunction called Oropharyngeal Dysphagia (OD) is caused by decreased muscle control, both in the throat and in the cheeks, tongue, and lips, resulting in a delay in oral transit time. It is a common symptom and has a negative impact on the quality of life of patients and their carers, particularly at a psychosocial level. (41,43)

Hypersalivation and sialorrhea appear not only in the pilot stages associated with bradykinesia of the muscles used in swallowing, but also in more advanced stages of disease progression, where they require a more complex treatment - swallowing exercises or fluid thickening. Some of the consequences associated with these swallowing problems are

malnutrition, dehydration, weight loss, difficulty in administering oral medication, or the most severe, aspiration pneumonia, which is one of the main causes of mortality in PD patients. (44)

l) Urinary problems

Lower urinary tract symptoms are quite common in Parkinson's disease, with an estimated prevalence between 25-70% of the patients. Urinary dysfunction is often caused by hyperactivity of the detrusor muscle or incomplete emptying of the bladder, leading to urgency and increased frequency of urination and nocturia, or even urinary incontinence. All these symptoms have a significant impact on the life of the patient and his caregiver, more specifically on the quality of sleep, falls or possible institutionalization. (45)

Urinary tract infections (UTIs) are one of the most frequent causes of hospitalization in PD patients. The risk of developing a UTI increases with age and is more common in women, but scientific evidence indicates that it is doubled in a patient with Parkinson's disease. These patients are more likely to contract these infections for several reasons, from urinary retention to excessive use of anticholinergic or antimuscarinic drugs, eventual catheterization, to hygienic factors, among many others. (44,46)

m) Mental Health Disorders/Neurobehavioral Disorders

Although they aren´t core symptoms in the diagnosis of the disease, neuropsychiatric signs are gaining recognition at a scientific level, as Parkinson's disease is increasingly being considered a neuropsychiatric disorder. As the disease evolves, mental health concerns increase as it progressively affects the quality of life of these patients and consequently their caregivers. (44)

Within this group of symptoms, we can divide them into several types: affect, perception, thinking and motivation. These include lack of emotional involvement or interest, also called apathy, mood disorders, depression and anxiety, cognitive impairment, also known as dementia, psychosis, impulsive control disorders, among others. These conditions are the most common non-motor symptoms associated with this disease, although they may be present throughout the course of the disease and may even appear before the diagnosis of PD. (47)

PD often culminates in dementia, which is a cognitive decline that affects a person's ability to plan and perform daily tasks. Later, it can also affect relationships with other people, as lack of expression and changes in voice make communication difficult. This cognitive decline is usually slow and unnoticed, but sometimes it may occur suddenly. It is important to monitor some risk factors, including visual hallucinations, the patient's age, and changes in some

biomarkers that are believed to be related to this cognitive impairment. The mechanisms underlying this disorder remain unclear, and further research is needed to better identify any evidence to support these predictions. (48)

Currently, the only drug approved for the treatment of dementia in PD is rivastigmine. Donepezil and galantamine are also used in off-label form and memantine is still being studied for this purpose. (44)

Neuropsychiatric symptoms are often unrecognized and untreated. Underreporting may occur due to lack of knowledge, stigma, or insufficient access to mental health care. Underdiagnosis of depression and anxiety is estimated to be about 50% in patients suffering from Parkinson's disease. Recognition of these symptoms is the first step to the optimization and thus the success of all treatment. Given the influence of these symptoms on disease progression, they should be formally evaluated by the neurologist every 6 to 12 months to assess and, if necessary, adjust the treatment plan. (44,48)

3.4.Parkinson's Disease in the World

Parkinson's Disease is quite common, affecting more than ten million people worldwide. Its high rates of disability, need for care and death are increasing faster when compared to other disorders in the same range. This disease is the fastest growing neurological condition, and it is the second most important neurodegenerative disorder in the elderly population, right behind Alzheimer's disease. (49)

In less than 20 years, the number of patients has doubled exponentially, which can be explained by the increased longevity and industrialization. It is the second most common age-related neurodegenerative disease in the world. Unlike other disorders, where growth decreases with improving socioeconomic status, in Parkinson's Disease this is not the case. (49,50)

With the global aging of the population, and consequently the increase of people aged 65 years and older, there is an exponential increase in patients with PD. It is estimated that, by 2040, the number of patients with Parkinson's will exceed twelve million. It is important to note that this disease does not only affect the elderly, as it sometimes appears before the age of fifty. (49,50)

3.5.Parkinson's disease in Portugal

Parkinson's disease has increased exponentially in recent decades and is likely to continue to do so. It appears, in most cases, after the age of sixty-five and, as it progresses, it becomes

increasingly disabling. Currently, this disease has around 20,000 patients in Portugal, however, this number tends to increase even more since this is one of the most aged countries in Europe, and this increases the probability of developing PD. (1)

3.6. Incidence of Parkinson's Disease

The risk of developing PD naturally increases with age and the highest percentage of those affected are aged over 60 years. However, there is a small part, about 5-10% of these patients, who develop this disease early, more specifically before the age of fifty. (24) When it occurs before the age of 21 years age it is called juvenile Parkinson's disease. This small percentage of early-onset forms of Parkinson's Disease (EOPD) is usually inherited. Therefore people must have a close family member with this disease, like a parent, sibling, or child. It is even thought that this disease may be associated with specific changes in genes. In most cases, the origin of the disease is unknown, but genetic, and environmental factors may have an influence. (2,51)

There are some studies, particularly in Portugal, who seek to identify a correlation between the development of mutations in certain genes and the development of Parkinson's Disease, but this work is very recent, so it is not yet possible to confirm these associations. (51)

Although age is the major risk driver for the developing of Parkinson's Disease, environmental and genetic factors also affect the predisposition and progression of the disease. Studies have already been carried out to test the exposures and their consequences, namely in terms of smoking and caffeine intake, to determine if there is a protective effect. (18)

Some studies indicate that men and people designated male at birth are more likely to develop this disease compared to women or people designated female at birth. (52) They even state that PD is twice as common in men than in women, in the general population. This corroborates that there is a protective effect of female hormones, and that environmental exposure to risk factors may be one of the causes of this male predisposition to the disease. (3)

3.7. Diagnosis of Parkinson 's disease

There are no laboratory tests for the diagnosis of Parkinson's Disease. The diagnosis is made through the analysis and observation of the patient's symptoms, and must be done by a specialist, usually a neurologist. It is clinical, subjective, and highly unspecific. Given the wide range of non-motor and motor symptoms observed in these patients, it is extremely difficult to

reach a proper decision. Although there are no tests that prove the diagnosis, they can be used to screen for other diseases with similar symptoms, thus proving the clinical diagnosis.

Given the complexity of the different clinical manifestations of the disease, the possible differential diagnoses must be reviewed to avoid a misdiagnosis. Dementia, hallucinations, delusions, confusion, depression and other psychological disorders, orthostatic hypotension, daytime sleepiness, sleep behavior disorder, urinary disorders, constipation, sexual dysfunction, are some of these symptoms. (2,3,53)

3.8. Treatments for Parkinson ’s disease

Although there is no cure, there are different treatment options to reduce the incidence of Parkinson’s disease. The scientific community can adopt two approaches: the implementation of adjustments in lifestyle that reduce behavioral and environmental risk factors, and the development of new drugs that act on this specific genetic mechanism. (16)

The main problem in the development of therapies that act in this progression is the lack of knowledge of the molecular events that lead to this neurodegeneration. However, these therapies are still being developed, even with limited results. (53)

It can also be considered surgery, which can significantly reduce the magnitude of the symptoms. Deep Brain Stimulation (DBS) is an option for patients who no longer respond to oral drugs. This surgical intervention consists of introducing electrodes that will provide continuous electrical impulses from the frontal lobe to the basal ganglia. Through this stimulation we will decrease motor fluctuations and, consequently, the dyskinesia and tremors that may arise from to medication. It is important to mention that, like any surgery, there are adverse reactions and associated complications, which may be noticed both in the short and long term. (54)

The goals of the therapy vary from person to person, so it is important to personalize the treatment to the needs of each patient. (55)

As there are limited drugs available for the treatment of this condition, the medical management of the symptoms becomes more complicated in an advanced stage of the disease progression. (3) The standard and most conventional initial therapy for these patients is Levodopa, a dopamine precursor, and the response to this therapy is generally good.

However, with the progression of the disease, patients begin to experience a decreased response to the prescribed medication. This results in a mixture of two phases: a phase of good response to therapy and a phase of poor response. These last phases reflect an increase in

involuntary movements among other motor complications. To manage these fluctuations, it is often necessary to add another drug. Other symptomatic treatments include the dopamine agonists – amantadine, apomorphine, bromocriptine, cabergoline, ropinirole, and the MAO inhibitors such as selegiline and rasagiline, and COMT inhibitors, entacapone and tolcapone. (49)

Benzodiazepines are widely used for anxiety but should be avoided in the elderly due to their tendency for falls and excessive sedation. Tricyclic antidepressants such as nortriptyline or amitriptyline, serotonin reuptake inhibitors such as fluoxetine or escitalopram, or even buspirone can be used in these patients. (56)

Exercise may have a central effect on depression, as it increases the release of beta-endorphins, the availability of brain neurotransmitters such as serotonin, dopamine and noradrenaline, and other brain-derived neurotropic factors. These changes can lead to improved self-esteem, self-evaluation, and a sense of accomplishment. (3,52,55)

3.9.Prognostic of Parkinson's Disease

As an extremely heterogeneous neurodegenerative disease, the diagnosis, prognosis, and progression assessment of Parkinson's disease remain solely clinical, presenting numerous challenges, such as the lack of unique biomarkers for this condition, the instability of clinical phenotypes, and the overlap of clinical findings with other neurological diseases. (57)
Parkinson itself is not fatal, but the complications that arise from this disease can be extremely serious and lead to death. (52) The consequences of Parkinson's, whether in terms of disability or even death, are escalating much faster compared to other neurological disorders. (58)

Currently the improvement of Parkinson's Disease is limited and relies on symptomatic treatment to improve its prognosis. Although animal models have provided valuable information about the pathogenic mechanisms underlying PD, the lack of models that recreate the complex pathophysiology of the disease delays the development of new therapies. (58)

4. Applications for Parkinson’s disease

With the growth in technology matters, several applications have emerged with the main objective of lighten the routine of a patient with Parkinson's Disease, which will ease the development and monitoring of symptoms associated with this condition. There are already scientific studies that prove its effectiveness in terms of following treatments more rigorously and maintaining a more organized lifestyle. (5)

Mitigating the consequences of the symptoms of this disease becomes a crucial task, so it is important to stimulate these abilities to slow their progression. After reviewing the literature about the disease, we collected all the symptoms that should be monitored daily through a software, for a better understanding of the disease. We concluded that for a better progression monitoring of sleep quality, communication, speech, swallowing and drinking control, mobility and dexterity, mood swings, and pain management should be possible.

a) Sleep Quality

We have several sleep-related problems, such as REM Behavior Disorder (RBD), sleep fragmentation, reduced sleep efficiency and excessive daytime sleepiness. In patients with Parkinson’s Disease these are some of the most frequent non-motor symptoms and the ones that impact the patients’ lives the most, as well as their families and/or caregivers. (59–61)

In addition to the numerous factors that affect brain function, namely neurotransmitters, in this disease, dopaminergic drugs are known to influence the regulation of sleep and wakefulness. It is thought that these disorders may be associated with dopamine deficiency. (59–61)

Sleep monitoring becomes essential to understand the impact of sleep cycle changes on the patient's daily life and, if necessary, to adapt its therapy to this problem. The initial goal is to improve sleep quality without using specific drugs for this purpose, since drugs developed to induce sleep may increase confusion, imbalance, and daytime sleepiness, thus increasing the risk of falls. We should then try to improve sleep hygiene, namely in terms of room temperature, regular sleep schedule and other habits to avoid near bedtime. All these interventions should be described in the software in order to allow the clinical team to monitor the quality of the patients' sleep and examine these different inputs to identify the source of the problem and treat it before it escalates, so that it has the least possible impact on the patient’s quality of life. (59–61)

b) Communication & Quality of Speech

The communication difficulties associated with PD, in terms of speech and language, are a significant factor that decreases the quality of life in these patients. These problems impact communication, whether with family, friends, colleagues or even the medical team. They can interfere with work and even limit social interactions. They can often lead to social withdrawal, social isolation, and stigmatization. Many people find that the Internet can be a useful way to stay connected with others when other forms of communication become more difficult. (31,62)

Mobile applications that monitor PD' symptoms should have a field that presents exercises to stimulate intonation and voice volume, which are extremely important items for correct and understandable communication. There are also some options that can remind patients to speak louder or slower, for example. All these features will help patients practice speaking and maintaining perceptible communication. (26,31,62)

c) Eating & Drinking

Problems associated with swallowing and dribbling of saliva were reported by patients with Parkinson's Disease. (26,63) It is important to identify this symptom, either through a clinical examination, evaluation of the swallowing process, or by following a standardized protocol, for instance, the EAT 10 - which is a tool that helps to assess the impact of dysphagia on patients' lives, so that measures can then be taken to help slow down the evolution of this problem and avoid more serious consequences. (64)

These patients tend to swallow less and less completely, which results in an accumulation of saliva in the mouth. To avoid this sensation, one suggestion is to suck on a hard candy, preferably without sugar, as it will stimulate the act of swallowing, and relieve the sensation of saliva accumulation. (63)

To improve these abilities, we can try exercises that facilitate the act of swallowing, for example exercises associated with the expiratory muscle's strength, which improves swallowing and promote coughing, to reduce the possible aspiration pneumonia. These patients should also try to change their diet. For example, those who cannot stop the intake of the drink, can try to thicker liquids, or replace them with solid food. It is also important that during mealtime this is the only focus, allowing greater concentration and avoiding mistakes that put patients at risk. (63,64)

d) Mobility Exercises

Patients with PD have deficits in motor function, such as gait, balance, and mobility impairments. Moreover, these disorders can be detected early in the course of the disease, and their decline can lead to disability. These factors highlight the need for complementary approaches, such as exercise, to treat this debilitating disorder. (65)

According to this study, physical activity can delay or reverse the degeneration of physical and psychological functions, as well as increase the quality of life of Parkinson's disease patients. It improves muscle strength, balance, gait, posture, and cognition. Thus, these results suggest that physical activity, namely aerobic training, may be a good strategy for these patients. (65,66)

It has also been scientifically proven that the motor function of a person with Parkinson's improves with exercise. However, to understand which of the several types of exercise is most effective, we need to compare the different approaches, since the progression of the disease varies from person to person, and each person reacts differently to various stimuli and exercises. Dancing, walking, or stretching are some of the safest and most feasible exercises for these patients. (65,67)

Given the clinical evidence and the importance of exercise, any application that monitors Parkinson’s disease should have parameterized alerts that suggest the practice of regular exercise and presents suggestions of exercises according to the skill to be trained, namely balance, flexibility, strength, mobility, or ease of movement training. Given the postural instability and muscular rigidity that are characteristic of PD, these capacities should be trained regularly so that it can help improve the symptoms and slow down the progression of the disease. (67)

In addition to promoting better symptom control, physical exercise decreases the risk of developing cardiovascular diseases, diabetes, obesity, osteoporosis, and psychological illnesses, thus allowing patients to have greater independence and quality of life.

e) Cognitive Rehabilitation

Although motor disorders respond well to dopaminergic therapy, cognitive symptoms, due to their complexity and variability, have not shown as much effectiveness in terms of pharmacological therapy. Therefore, research studies of non-pharmacological treatments have been carried out to improve cognitive capacity, as an alternative or in conjunction with drugs already used. (68)

The neurologist in charge, together with the rest of the medical team, should establish the therapeutic goals and share the treatment plan in the software so that both the patient and the caregiver can access it. This neuropsychological rehabilitation has interventions at the cognitive, emotional, and psychosocial function levels, and is also called Cognitive Behavioural Therapy (CBT). It may include exercises to train cognitive function, new strategies to manage stress, sleep, and social functioning, and instruction in the use of other assistive devices. It is mandatory that the patient understands the importance of this therapy in the management of PD and optimizes their life so that rehabilitation becomes part of their routine. Both the family and the caregiver should work together to encourage and motivate the patient to continue working in these skills. (69)

f) Healthy Lifestyle

Several studies have been performed to analyze the influence of environment, lifestyle, diet, physical activity, and sleep on the course of the disease. These studies have been conducted suggesting a positive association between diets and their metabolic profiles with the risk of developing PD, especially in men, regarding caffeine consumption, increased uric acid, and cholesterol levels. (60)

There is growing evidence supporting the protective association between eating a balanced diet and the decreased development of Parkinson’s Disease. One example is the Mediterranean diet, which should be based on fresh products, such as fruits and vegetables, low-processed foods, and a small proportion of simple carbohydrates. On the other hand, these studies also suggest that nutrition and metabolic conditions, such as diabetes or obesity, may increase the risk of developing PD after middle age. (60)

Some studies indicate that a high intake of fruits, vegetables, and fish is inversely associated with the risk of developing Parkinson's, since they lead to a decrease in the functional decline associated with ageing. There is also scientific evidence suggesting that caffeine is neuroprotective since it reduces dopaminergic toxicity and slows the progression of the disease.

The neuroprotective action of black tea and green tea, through polyphenols, has also been studied and is thought to help delay age-related deficits and neurodegenerative diseases. As for alcohol, there is still no consensual opinion, with studies suggesting that alcohol consumption may have neuroprotective effects, and others suggesting that increased consumption of alcoholic beverages may increase the risk of developing PD. (70)

g) Mood Tracker

Among the behavioral disorders associated with Parkinson's Disease, mood disorders are quite common and can occur at any stage of the disease or even precede the motor symptoms. From depression, anxiety, stress, apathy, these symptoms impact the quality of life, affecting daily tasks. Their diagnosis, classification, evaluation, and treatment remain a challenge, due to the overlapping of symptoms among the different neurological disorders. (71)

Some of the issues to consider before choosing a treatment include: (A) the possible existence of other comorbidities that may be causing these problems, such as anaemia or several infections, (B) reviewing all medication to understand if any of these drugs have interference or may cause these symptoms, (C) understanding if this problem is associated with motor fluctuations, i.e. by adjusting the dose and frequency of medication and reducing motor fluctuations we can also reduce stress and anxiety in these patients, (D) before considering pharmacological treatment we should first try a lifestyle approach, i.e. a non-pharmacological approach, (E) if the symptoms are a consequence of taking medication, we should reduce the dosage of the drug, change the drug for one with a similar effect or even withdraw it, (F) finally, ensure a good diagnosis of these symptoms, so that the pharmacological treatment is the most appropriate. (44)

h) Stress Management

Psychological interventions are essential for the treatment of these symptoms, as they help the patient cope with stress and anxiety. Some of these strategies include relaxation, cognitive restructuring, as well as behavioral analysis of the different situations and their management adapted to the disease. Other alternatives include meditation, stretching, singing, dancing, painting, among other activities.

i) Pain Management

Associated with Parkinson's disease is a decrease in quality of life, often related with motor symptoms, but also with non-motor symptoms. Although pain is common to several diseases, it is one of the most frequent complaints in these patients, affecting more than 70% of this population, especially when underdiagnosed and mistreated. (72)

Pain in PD' patients is assessed through a calibrated and validated questionnaire specific for this pathology, with the aim of assessing pain quantitatively and qualitatively. Motor fluctuations represent one of the main causes of pain, but it can be multifactorial, being

associated with other diseases or even with common problems not related to Parkinson's, such as joint or spinal problems. Thus, for the proper management of this disease and, inherently, for an improvement in overall quality of life, all forms of pain must be identified, diagnosed, and treated accordingly. One of the main problems in this field is the lack of association of pain with the disease itself, which leads patients to consult other specialists when they should really consult a neurologist, which will hinder the correct treatment of the underlying pathology. (72)

The most common pain management therapy are dopaminergic drugs, since this pain can be associated with dopaminergic depletion, thus improving akinesia and/or stiffness. Other drugs used to combat pain are NSAIDs, non-steroidal anti-inflammatory drugs, such as ibuprofen and diclofenac, but also metamizole, and cyclooxygenase two inhibitors, particularly nimesulide and etoricoxib. Other analgesics include paracetamol, pregabalin, and amitriptyline, the latter often used for neuropathic pain. (73)

j) Family/ Carers zone

Any application for this purpose should contain a section exclusively dedicated to caregivers, family, and anyone else who has regular contact with the patient. Based on existing courses for informal caregivers, we think it is pertinent to adapt this information for Parkinson's disease in specific. As such, we suggest the creation of an orientation course for informal caregivers of Parkinson's Disease patients. This course should aim to support the needs of this community of caregivers, either by promoting proximity between health professionals and caregivers, or by gaining the knowledge and confidence to take the necessary steps to provide the highest quality of life possible for these patients.

The purpose of this course is to rise awareness of the importance of educating these caregivers; to promote the empowerment of these caregivers to assist the patient in daily tasks, if necessary; to promote the monitoring of the symptoms inherent to PD; to ensure the correct intake of medication, and also to allow the interaction of these caregivers with health professionals in some particular items where another type of support and knowledge is needed.

k) Crowd Knowledge

Another extremely important feature of this mobile application is the existence of a sharing channel within this community. Here, patients, caregivers, family, as well as the medical team itself can share their opinion, content, achievements, and can communicate with each other. That way, these patients can talk without having to travel, and have access to current information and trends without having to leave home.

l) Clinical zone

This is an important section in any software, as it presents a compilation of information about the diagnosis and treatment of the disease, as well as tips and preventive measures to adopt during this journey. It includes topics such as active lifestyle, balanced diet, physical exercise, cognitive stimulation, among others. The most recent articles and news about these topics are also made available. An extremely positive point is the availability of these materials in different formats, namely as videos, podcasts, or even newspapers, to stimulate their viewing by everyone. This content is available for both patients and caregivers.

m) Therapist Support

Talking to a specialist about physical, psychological, and social problems is one of the most key factors in managing this disease. In this sense, specialists help on a practical level, instructing the patient on how to act and react towards the challenges that arise in daily tasks, and adjusting the pharmacological and other treatments according to the patient's response. The frequency of this discussion depends on the evolution of symptoms and the patient's own needs. (56)

As patients may not spontaneously report all symptoms, the opinion and sharing of relatives and/or caregivers is crucial to understand the level of distress and impact on quality of life, and to get an overview of the magnitude of these symptoms. Thus, in this space of the app it is possible to contact the medical team directly and clarify doubts or highlight behavioral changes that need further supervision. Although this communication channel is available both for patients and for the caregivers themselves, there are two simultaneous chats with the specialist, to maintain the confidentiality of both conversations. (56)

n) Symptom Tracker

As we have seen before, numerous motors and non motor symptoms are associated with Parkinson, and often the treatment of the disease itself involves treating or correcting these symptoms, preventing them from having worse effects. Thus, it is extremely important to monitor all symptoms, to allow adjustment of medication and dose depending on the magnitude of these symptoms. (24)

One of the most characteristic symptoms of PD is resting tremor. Therefore, in this application it will be possible to determine the frequency of this tremor. You only have to hold the mobile phone down in your hand and wait about 1 minute for the measurement. These data are analyzed and adjusted automatically and becomes available in a matter of seconds. This

measurement is taken periodically throughout the day, and the app sends an alert so that the patient remembers to measure it. For those using smartwatches, the measurement is done automatically, and it is also possible to detect and quantify the slowness of movements. (24) Some of the symptoms to be monitored are, for example, nocturia and incontinence, which cause sleep fragmentation, thus impacting the quality of life of patients. These problems have extremely limited treatment options, and sometimes poorly tolerated by patients. From non-pharmacological measures, such as reducing fluid intake a few hours before bedtime and exercise, to taking dopamine agonist drugs, and finally, deep brain stimulation in more advanced stages of the disease. (45)

Currently, there are a few studies that effectively explore the role of intestinal symptoms in the initial stages of Parkinson's Disease. Thus, by detecting gastrointestinal symptoms in these stages, it may be possible to associate them with the initial pathophysiological changes and take the necessary preventive measures or initiate treatment, if necessary. Therefore, early detection of these symptoms and consequent monitoring is essential for improving quality of life. Diet can even have a positive impact on the bioavailability of the drugs themselves, thus improving response to therapy. (41)

As we know, PD symptoms vary from patient to patient, and fluctuate throughout the day. Through this app it is also possible to monitor non-motor symptoms. Patients receive two alerts, one in the morning and another at the end of the day to quantitatively evaluate these symptoms, namely, constipation, ease of walking, falls, ease of getting up, nausea, pain, sleep time, communication, swallowing, among others. The software itself converts the data into a visual representation that makes it easier to identify fluctuations.

5. How to live with Parkinson – New Application Idea

After studying the physiopathology of the disease, its progression, the motor and non-motor symptoms that characterize it and the softwares that are available to monitor them we realized that there was no single mobile application that gathered all the necessary features, such as non-pharmacological intervention measures, rehabilitation exercises, a direct connection with the medical team and that monitored all the symptoms and collected the data from this screening.

This app was created to solve the lack of information and data, and to help the medical team make more informed decisions about the therapy to be adopted according to the intensity of the symptoms and the impact on the patient's quality of life. On the other hand, given the lack of studies about this disease, it is important to analyze data from different patients to create a validated software that can accurately read the different inputs and reach reliable conclusions.

This way we developed an innovative and comprehensive platform that contains all the elements we believe are important for the daily routine of a person with Parkinson's disease, which we called "How to live with Parkinson's". In this tool, new solutions and interventions emerge that we believe are fundamental to follow up and monitor the quality of life of these patients, so that it is possible to measure the impact of the disease, not only in the life of the people affected but also in the lives of those around them.

Some of the functions of this software are simple monitoring of the patient's functional capacity, from correct medication intake to quantifying the intensity of symptoms and their implications on quality of life - changes in the sleep cycle, pain, stress and anxiety management, difficulty when drinking or eating, changes in communication and speech quality, and more.

The key differentiating factor of this new platform compared to the ones already on the market will be the existence of all the features considered essential in a single software. There will be a direct communication channel between the patient and the doctor, and also between the doctor and the caregiver, which will be used to clarify doubts or even to monitor the situation in a more informal way when compared to a follow-up appointment.

Another unique feature of this software is the control over the data collected in real time. During the monitoring of these symptoms, when the data exceeds a certain threshold previously established by the medical team in charge, both these health professionals and the caregiver immediately receive an alert and a follow-up appointment is automatically scheduled for the next available time slot. Depending on the severity of the observed alteration, more effective interventions can also be performed, such as calling the medical emergency team. Through this app it is now possible to fully monitor the entire progression of the disease, which makes it

easier and more effective to adjust the medication and lifestyle to the patient's own functional capacity. This agility of resolution of these problems avoids unnecessary visits to the Health Units, thus contributing to a less burden of these services. This way, we save essential resources such as time and money and, above all, we fulfill the main goal of slowing down the progression of the disease and improving the quality of life not only of the patient but also of those who care for them.

Through this application it will also be possible to do a better medication management, since we can compare the time of medication intake with observed symptom changes, the so-called motor fluctuations, and easily make an adjustment to decrease the occurrence of these events.

Considering the characteristics of the disease, the scientific evidence, and the existing softwares, we conducted a systematic analysis of what was available, the result of which was the table presented. Considering this, we made an integrative proposal that included everything that exists and everything that should exist to help patients live with the disease. We have with these two purposes, to allow knowledge about a specific patient, monitoring their symptoms and their quality of life, but also to increase the existing knowledge about this disease in general.

This will contribute to better disease management by collecting data that will increase the scientific evidence around this subject.

Table 1: Comparison of the different existing symptom monitoring applications and the software proposed in this work, named “How to live with Parkinson.”

		Sleep Quality	Communication	Eating & Drinking	Mobility Exercises	Cognitive Rehabilitation	Healthy Lifestyle	Mood Tracker	Stress Management	Pain Management	Carers Zone	Crowd Knowledge	Clinical Zone	Therapist Support	Symptom Tracker
1	Pzizz	1													
1	Sleepio	1													
1	Voice Analyst		1												
2	Cove					1		1							
1	Swallow Prompt			1											
2	Peak app		1			1									
1	Luminosity					1									
3	Beats Medical		1		1	1									
1	Mood tracker							1							
1	Breath2Relax								1						
1	Pain Management Plan									1					
1	APDA Symptom Tracker												1	1	1
2	Bout		1		1										1
1	CogniFit					1									
1	StudyMyTremor														1
1	Loud & Clear		1												
4	My Parkinson's Disease Manager							1			1		1		1
3	Parkinson Exercises Tablet		1		1	1									
14	How to live with Parkinson?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Total	3	7	2	4	7	1	4	2	2	2	1	3	2	5

A prototype of the software can be seen in the appendixes.

6. Implications of monitoring the progression of Parkinson’s disease

The software we propose in this paper should provide a holistic support for all patients, at any stage of the disease, and to the different stakeholders, with the main purpose of supporting the entire community. Through the collection of this data, besides having an overview of how the natural evolution of the disease takes place, namely how symptoms evolve and what is their impact on the quality of life of these patients. It is through this data that it becomes possible to develop a scientifically validated algorithm that serves as a basis for diagnosis and treatment for medical staff and provides scientific evidence to identify risk factors that may be at the origin of the disease and that might influence the progression of symptoms, alerting to their future monitoring. As stated before, this disease has only begun to be significantly studied quite recently, so there is a lack of data and studies to allow the establishment of consensual conclusions.

Understanding risk factors and correlations between symptoms and signs and the occurrence of Parkinson's disease may facilitate the identification of neurological disorders, allowing for early detection of the disease and its management, or even potential prevention, when risk factors can still be modified and changed. (60)

In more advanced stages of disease progression, monitoring can facilitate and allow faster treatment of more severe conditions, it can decrease the length of hospitalization since all the data necessary for a diagnosis and treatment are already available, reduce the risk of readmissions since we will focus on prevention rather than treatment, and finally, it can also help identify a high-risk patient by detecting signs of deterioration in the patient's condition more easily and quickly.

7. Conclusion

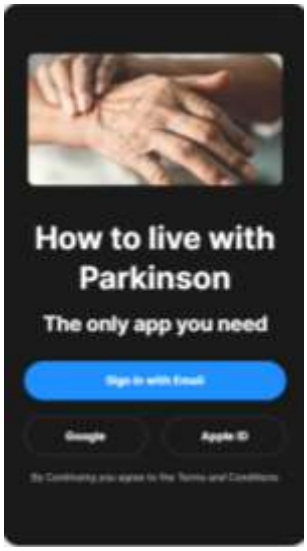
Predictive analytics data in healthcare through Artificial Intelligence algorithms will soon become an indispensable tool. From helping physicians plan their interventions faster and more effectively, to achieving better outcomes, these algorithms are extremely valuable. (3)
One of the uses of this application is to monitor and treat symptoms in real time, which is then analyzed through a visual representation, which will be shared with the clinical staff that is following the patient. By analyzing this plot, which shows the real-time changes in the symptoms, and based on existing scientific evidence, clinicians can try to adjust the therapy. Knowledge of both motor and non-motor symptoms and a multidisciplinary approach to their treatment are essential to optimize their monitoring and slow the progression of the disease, therefore reducing its impact on patients' quality of life.

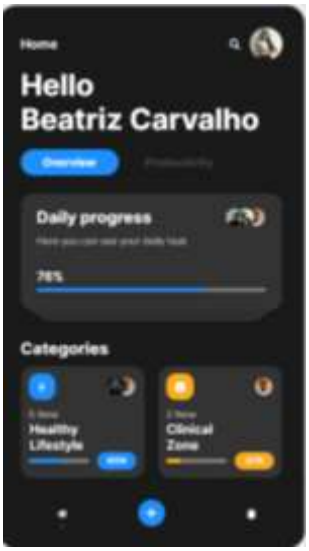
The development of digital cognitive tests, the evolution of computerized tests that are automatically completed in real time, and the existence of mobile devices that allow assessment of cognitive functioning in daily tasks provide an excellent opportunity to improve clinical management and to obtain more sensitive results to be used in clinical trials. (73)

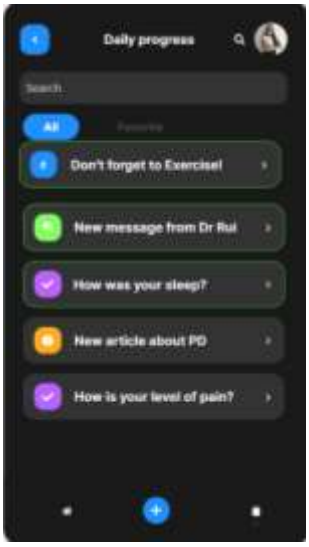
In the future, these innovations will become standard procedure, as technological innovations and increased access to the Internet and many digital devices, including mobile phones or computers, will make it possible to reach a huge part of the population. However, all data and tests must be standardized, tested and validated to be used by everyone and to recognize any information. This is why we need a large amount of data to "train" the algorithm to interpret and verify different inputs and this is only possible by constantly monitoring these symptoms. (43)

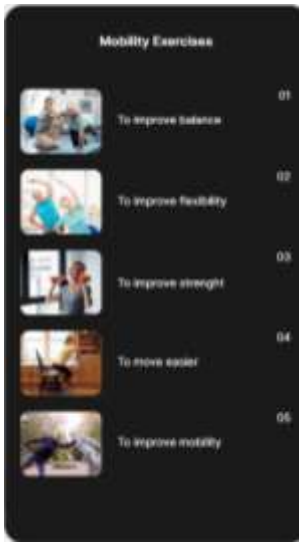
One of the limitations of this application is the fact that it was developed only for Parkinson's disease, so its use is limited to this pathology, to these patients, caregivers and doctors working in this specialty. On the other hand, although it is an emerging disease and there are increasingly scientific articles about it, the characteristic symptoms are very unspecific, since they occur in several other pathologies, so it is important to monitor them to establish the correct diagnosis. By the existence of these less specific symptoms, other pathologies with similar symptoms can take advantage of several features of the app.

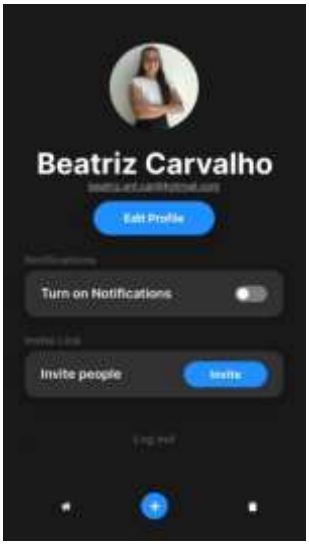
8. Appendixes











9. Bibliography

1. Doença de Parkinson ″é um peso para os sistemas de saúde, doentes, famílias e cuidadores″ [Internet]. [cited 2023 Jun 29]. Available from: https://www.dn.pt/especiais/saude-e-sustentabilidade/doenca-de-parkinson-e-um-peso-para-os-sistemas-de-saude-doentes-familias-e-cuidadores-15446172.html

2. Parkinson's disease | Hospital da Luz [Internet]. [cited 2023 Jun 29]. Available from: https://www.hospitaldaluz.pt/en/health-dictionary/parkinson-disease

3. Radhakrishnan D, Goyal V. Parkinson's disease: A review. Neurol India. 2018;66(7):26.

4. Cabreira V, Massano J. Doença de Parkinson: Revisão Clínica e Atualização. Acta Med Port. 2019 Oct 1;32(10):661–70.

5. Erich Fonoff. Aplicativos para facilitar a rotina do Parkinsoniano. 2019.

6. IBM Corporation. What is predictive analytics? | IBM [Internet]. 2019 [cited 2023 Jun 19]. p. 5–12. Available from: https://www.ibm.com/topics/predictive-analytics

7. Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, et al. Artificial intelligence in healthcare: past, present, and future. Stroke Vasc Neurol. 2017 Dec;2(4):230–43.

8. Hernandez I, Zhang Y. Using predictive analytics and big data to optimize pharmaceutical outcomes. American Journal of Health-System Pharmacy. 2017 Sep 15;74(18):1494–500.

9. Ralabs. Predictive analytics in healthcare: all you need to know. 2023 Apr 13 [cited 2023 Jun 28]; Available from: https://ralabs.org/all-you-need-to-know-about-predictive-analytics-in-healthcare/

10. David G, Smith-McLallen A, Ukert B. The effect of predictive analytics-driven interventions on healthcare utilization. J Health Econ. 2019 Mar;64:68–79.

11. Abouelmehdi K, Beni-Hessane A, Khaloufi H. Big healthcare data: preserving security and privacy. J Big Data. 2018 Dec 9;5(1):1.

12. DiGiorgio AM, Ehrenfeld JM. Artificial Intelligence in Medicine & ChatGPT: De-Tether the Physician. J Med Syst [Internet]. 2023 Dec 1 [cited 2023 Jun 28];47(1). Available from: https://www.ama-assn.org/practice-management/digital/why-generative-ai-chatgpt-cannot-replace-physicians

13. Will AI Eventually Replace Doctors? [Internet]. [cited 2023 Jun 28]. Available from: https://insight.kellogg.northwestern.edu/article/will-ai-replace-doctors

14. Mazzoni P, Shabbott B, Cortés JC. Motor control abnormalities in Parkinson's disease. Cold Spring Harb Perspect Med. 2012;2(6).

15. Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. J Parkinsons Dis. 2018 Dec 18;8(s1):S3–8.

16. Simon DK, Tanner CM, Brundin P. Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. Clin Geriatr Med. 2020 Feb;36(1):1–12.

17. Beitz JM. Parkinson s disease a review. Frontiers in Bioscience. 2014;S6(1):S415.

18. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol. 2020 Feb;19(2):170–8.

19. Nancy Hammond, Kristeen Cherney. The 5 Stages of Parkinson's. Healthline. 2021 Jul;

20. Five Stages of Parkinson's · Parkinson's Resource Organization [Internet]. [cited 2023 Jun 28]. Available from: https://www.parkinsonsresource.org/news/articles/five-stages-of-parkinsons/

21. Dementech Neurosciences. What are the 5 stages of Parkinso's Disease? 2022 Nov 10;

22. Clarke CE, Patel S, Ives N, Rick CE, Woolley R, Wheatley K, et al. Clinical effectiveness and cost-effectiveness of physiotherapy and occupational therapy versus no therapy in mild to moderate Parkinson's disease: a large pragmatic randomised controlled trial (PD REHAB). Health Technol Assess (Rockv). 2016 Aug;20(63):1–96.

23. Stages of Parkinson's | Parkinson's Foundation [Internet]. [cited 2023 Jun 29]. Available from: https://www.parkinson.org/understanding-parkinsons/what-is-parkinsons/stages

24. Parkinson's Disease: What It Is, Causes, Symptoms & Treatment [Internet]. [cited 2023 Jun 28]. Available from: https://my.clevelandclinic.org/health/diseases/8525-parkinsons-disease-an-overview

25. Dirkx MF, Bologna M. The pathophysiology of Parkinson's disease tremor. J Neurol Sci. 2022 Apr;435:120196.

26. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. J Neurochem. 2016 Oct;139:318–24.

27. Ferreira-Sánchez M del R, Moreno-Verdú M, Cano-de-la-Cuerda R. Quantitative Measurement of Rigidity in Parkinson's Disease: A Systematic Review. Sensors. 2020 Feb 6;20(3):880.

28. Gandolfi M, Geroin C, Dimitrova E, Boldrini P, Waldner A, Bonadiman S, et al. Virtual Reality Telerehabilitation for Postural Instability in Parkinson's Disease: A Multicenter, Single-Blind, Randomized, Controlled Trial. Biomed Res Int. 2017;2017:1–11.

29. Schlenstedt C, Paschen S, Kruse A, Raethjen J, Weisser B, Deuschl G. Resistance versus Balance Training to Improve Postural Control in Parkinson's Disease: A Randomized Rater Blinded Controlled Study. PLoS One. 2015 Oct 26;10(10):e0140584.

30. Dashtipour K, Tafreshi A, Lee J, Crawley B. Speech disorders in Parkinson's disease: pathophysiology, medical management, and surgical approaches. Neurodegener Dis Manag. 2018 Oct;8(5):337–48.

31. The Michael J. Fox Foundation. Speech & Swallowing Problems. Parkinson's Research.

32. Speech Characteristics of Parkinson's Disease [Internet]. [cited 2023 Jun 28]. Available from: https://www.healthline.com/health/parkinsons/speech-characteristics-of-parkinsons-disease

33. 10 early symptoms of Parkinson's | Parkinson's UK [Internet]. [cited 2023 Jun 28]. Available from: https://www.parkinsons.org.uk/information-and-support/your-magazine/tips/10-early-symptoms-parkinsons

34. Gros P, Videnovic A. Overview of Sleep and Circadian Rhythm Disorders in Parkinson Disease. Clin Geriatr Med. 2020 Feb;36(1):119–30.

35. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev. 2017 Oct;35:33–50.

36. Zuzuárregui JRP, During EH. Sleep Issues in Parkinson's Disease and Their Management. Neurotherapeutics. 2020 Oct 7;17(4):1480–94.

37. Tarakad A, Jankovic J. Anosmia and Ageusia in Parkinson's Disease. In 2017. p. 541–56.

38. Sheng MZ, Fang TC, Chen YH, Chang MH, Yang CP, Lin CH. Is either anosmia or constipation associated with cognitive dysfunction in Parkinson's disease? PLoS One. 2021 Jun 4;16(6):e0252451.

39. Poirier AA, Aubé B, Côté M, Morin N, Di Paolo T, Soulet D. Gastrointestinal Dysfunctions in Parkinson's Disease: Symptoms and Treatments. Parkinsons Dis. 2016;2016:1–23.

40. Warnecke T, Schäfer KH, Claus I, Del Tredici K, Jost WH. Gastrointestinal involvement in Parkinson's disease: pathophysiology, diagnosis, and management. NPJ Parkinsons Dis. 2022 Mar 24;8(1):31.

41. Yemula N, Dietrich C, Dostal V, Hornberger M. Parkinson's Disease, and the Gut: Symptoms, Nutrition, and Microbiota. J Parkinsons Dis. 2021 Oct 12;11(4):1491–505.

42. Armstrong RA. Visual signs and symptoms of Parkinson's disease. Clin Exp Optom. 2008 Mar 1;91(2):129–38.

43. Ciucci M, Grant L, Rajamanickam E, Hilby B, Blue K, Jones C, et al. Early Identification and Treatment of Communication and Swallowing Deficits in Parkinson Disease. Semin Speech Lang. 2013 Oct 28;34(03):185–202.

44. Gilbert R, Khemani P. Treatment of Advanced Parkinson's Disease. J Geriatr Psychiatry Neurol. 2022 Jan 29;35(1):12–23.

45. Batla A, Phé V, De Min L, Panicker JN. Nocturia in Parkinson's Disease: Why Does It Occur and How to Manage? Mov Disord Clin Pract. 2016 Sep;3(5):443–51.

46. Hogg E, Frank S, Oft J, Benway B, Rashid MH, Lahiri S. Urinary Tract Infection in Parkinson's Disease. J Parkinsons Dis. 2022 Apr 5;12(3):743–57.

47. Weintraub D, Aarsland D, Chaudhuri KR, Dobkin RD, Leentjens AF, Rodriguez-Violante M, et al. The neuropsychiatry of Parkinson's disease: advances and challenges. Lancet Neurol. 2022 Jan;21(1):89–102.

48. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, et al. Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers. 2021 Jul 1;7(1):47.

49. Cacabelos R. Parkinson's Disease: From Pathogenesis to Pharmacogenomics. Int J Mol Sci. 2017 Mar 4;18(3):551.

50. Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. J Parkinsons Dis. 2018 Dec 18;8(s1):S3–8.

51. Bras J, Guerreiro R, Ribeiro M, Morgadinho A, Januario C, Dias M, et al. Analysis of Parkinson disease patients from Portugal for mutations in SNCA, PRKN, PINK1 and LRRK2. BMC Neurol. 2008 Dec 22;8(1):1.

52. Parkinson's Disease: Causes, Symptoms, and Treatments | National Institute on Aging [Internet]. [cited 2023 Jun 29]. Available from: https://www.nia.nih.gov/health/parkinsons-disease

53. Cabreira V, Massano J. Doença de Parkinson: Revisão Clínica e Atualização. Acta Med Port. 2019 Oct 1;32(10):661–70.

54. Troche MS, Brandimore AE, Foote KD, Okun MS. Swallowing, and deep brain stimulation in Parkinson's disease: A systematic review. Parkinsonism Relat Disord. 2013 Sep;19(9):783–8.

55. Bloem BR, Okun MS, Klein C. Parkinson's disease. The Lancet. 2021 Jun;397(10291):2284–303.

56. Walsh K, Bennett G. Parkinson's disease and anxiety. Postgrad Med J. 2001 Feb 1;77(904):89–93.

57. Gramotnev G, Gramotnev DK, Gramotnev A. Parkinson's disease prognostic scores for progression of cognitive decline. Sci Rep. 2019 Nov 25;9(1):17485.

58. World Health Organization. Parkinson disease [Internet]. 2022 [cited 2023 Jun 29]. Available from: https://www.who.int/news-room/fact-sheets/detail/parkinson-disease

59. Stavitsky K, Cronin-Golomb A. Sleep Quality in Parkinson Disease. Cognitive and Behavioral Neurology. 2011 Jun;24(2):43–9.

60. Reichmann H, Csoti I, Koschel J, Lorenzl S, Schrader C, Winkler J, et al. Life style and Parkinson's disease. J Neural Transm. 2022 Sep 23;129(9):1235–45.

61. Stefani A, Högl B. Sleep in Parkinson's disease. Neuropsychopharmacology. 2020 Jan 24;45(1):121–8.

62. Rohl A, Gutierrez S, Johari K, Greenlee J, Tjaden K, Roberts A. Speech dysfunction, cognition, and Parkinson's disease. In 2022. p. 153–73.

63. Speech & Swallowing Issues | Parkinson's Foundation [Internet]. [cited 2023 Jun 29]. Available from: https://www.parkinson.org/understanding-parkinsons/non-movement-symptoms/speech-swallowing

64. Maurer Costa E. Caracterização do Risco de Disfagia em Paciente com Doença de Parkinson. [São Paulo]: Universidade Federal de São Paulo - UNIFESP; 2021.

65. Rawson KS, McNeely ME, Duncan RP, Pickett KA, Perlmutter JS, Earhart GM. Exercise and Parkinson Disease: Comparing Tango, Treadmill, and Stretching. Journal of Neurologic Physical Therapy. 2019 Jan;43(1):26–32.

66. Wu PL, Lee M, Huang TT. Effectiveness of physical activity on patients with depression and Parkinson's disease: A systematic review. PLoS One. 2017 Jul 27;12(7):e0181515.

67. Ellis TD, Colón-Semenza C, DeAngelis TR, Thomas CA, Hilaire MH Saint, Earhart GM, et al. Evidence for Early and Regular Physical Therapy and Exercise in Parkinson's Disease. Semin Neurol. 2021 Apr 19;41(02):189–205.

68. Glizer D, MacDonald PA. Cognitive Training in Parkinson's Disease: A Review of Studies from 2000 to 2014. Parkinsons Dis. 2016;2016:1–19.

69. Zhang Q, Aldridge GM, Narayanan NS, Anderson SW, Uc EY. Approach to Cognitive Impairment in Parkinson's Disease. Neurotherapeutics. 2020 Oct 17;17(4):1495–510.

70. Seidl SE, Santiago JA, Bilyk H, Potashkin JA. The emerging role of nutrition in Parkinson's disease. Front Aging Neurosci. 2014 Mar 7;6.

71. Tan LCS. Mood disorders in Parkinson's disease. Parkinsonism Relat Disord. 2012 Jan;18:S74–6.

72. Raza C, Anjum R, Shakeel N ul A. Parkinson's disease: Mechanisms, translational models, and management strategies. Life Sci. 2019 Jun;226:77–90.

73. Buhmann C, Kassubek J, Jost WH. Management of Pain in Parkinson's Disease. J Parkinsons Dis. 2020 Sep 1;10(s1):S37–48.