6

STAT-ON™: The Holter for Parkinson's Disease Motor Symptoms. Real Use Cases in Clinical Praxis

Núria Caballol* [1,2], Angels Bayés[2], Anna Planas-Ballvé[1], Tània Delgado[3], Asunción Avila[1], Alexandra Pérez-Soriano[2,12], López-Ariztegui Núria[4], Sònia Escalante[5], Diego Santos-Garcia[6,13], Jaime Herreros[7], Iria Cabo[8], Jorge Hernandez-Vara[9], José Maria Barrios[10], Lucía Triguero[10], Alvaro García-Bustillo[11], and Esther Cubo[11]

[1]Departament de Neurologia, Complex Hospitalari Moisès Broggi, Sant Joan Despí, Spain
[2]Unitat de Parkinson i Transtorns de Moviment, Centro Médico TEKNON, Barcelona, Spain
[3]Hospital Parc Taulí, Sabadell, Spain
[4]Unidad de Trastornos del Movimiento, Hospital Universitario de Toledo, Spain
[5]Hospital Verge de la Cinta, Tortosa, Spain
[6]CHUAC – Complejo Hospitalario Universitario de A Coruña, Spain
[7]Hospital Universitario Infanta Leonor, Madrid, Spain
[8]Complexo Hospitalario Universitario de Pontevedra, Spain
[9]Departamento de Neurología, Grupo de Investigación Enfermedades Neurodegenerativas, Campus Universitario Vall d'Hebrón, Barcelona, Spain
[10]Unidad de Trastornos del Movimiento, Hospital Universitario Virgen de las Nieves, Granada, Spain
[11]HUBU – Hospital Universitario de Burgos, Spain
[12]Fundació de Recerca Clinic Barcelona, Hospital Clinic de Barcelona, Spain
[13]Departamento de Neurología, Hospital San Rafael, A Coruña, Spain
(*) Chapter coordinator

Abstract

As part of the introduction and diffusion strategy of the STAT-ON™ device among neurologists and professionals, treating patients affected by Parkinson's disease, a number of experiences have been promoted in several hospitals and movement disorders units.

The present chapter explains 13 real use cases experimented in Spanish hospitals, mainly in the period 2020–2021, using the device to help the professionals with current treatment activity. In the totality of the presented cases, advantages have been obtained with the use of STAT-ON™. Details are reported in the following sections.

6.1 Introduction

This chapter presents a series of real clinical use cases developed over the last 2 years, including the use of the STAT-ON™, as part of the care and treatment process provided to various patients with Parkinson's disease.

As can be seen in the affiliation of the different authors, the collaborating hospitals and involved movement disorder units and services are distributed throughout the Spanish geography. These selected experiences are part of the introduction and dissemination process of the new STAT-ON™ technology in the regular neurologists' medical activity to treat already diagnosed patients with Parkinson's disease.

The previous chapters presented the complete process through which important scientific and technological results, materialized in the REMPARK project, became a class IIa medical device ready to be introduced to the market. This process means that a series of challenges and requirements of the process itself has been covered (scientific-technological quality, safety of use, adaptation to existing regulations, etc.) leaving, nevertheless, a very important aspect for this type of product, which consists of its acceptance for being used in medical practice by neurologists and professionals. It is very important, therefore, that STAT-ON™ can prove its usefulness, as a complementary technology, when used in the patient care process to provide relevant and decisive information for improving therapies.

The chapter has been coordinated by Dr. Núria Caballol and the authors, responsible for each use-case, are referred at the beginning of each section.

An attempt has been made that the different cases have a similar structure, which focuses on the presentation of the personal histories and those referring to the Parkinson's disease of each one of the patients. A presentation

of their condition is made according to the physical examination carried out, which in many cases (when the doctor considers it necessary) includes the result of various applied scales and tests. This is followed by the objective pursued, for each case, with the use of the STAT-ON™.

Results obtained are presented, showing relevant parts of the reports generated by the device, which allows addressing a series of discussions and conclusions related to each specific case, and which try to highlight the benefits obtained through the use of the technology. In many cases, this opens the door to being able to carry out an improved screening process, an improvement in the treatment, a better therapeutic adjustment, or the advanced identification of a series of characteristics related to the disease.

As a relevant conclusion, it is worth saying that the use of the STAT-ON™ device contributes to a better knowledge and understanding of the disease by the patients, helping them to be more aware of their condition (representing, also, an increase in the patients' empowerment level).

It is necessary to mention that, as the use cases are real, some of the presented figures, containing parts of the STAT-ON™ generated reports, are in Spanish since this is the language used by the authors in their contributing hospitals.

6.2 Early Detection of Motor Fluctuations

Responsible professional: Dr. Angels Bayés.
Unitat de Parkinson. Centro Médico TEKNON. Barcelona.

Personal history: This 65-year-old man worked as a commercial director in a data protection company. He has the habit of doing sports frequently and intensively. In 2013 he interrupted his sports activity due to a knee injury. Past clinical history includes olfactory dysfunction since many years, viral pericarditis in 1986, and surgically treated meniscopathy.

Parkinson's disease history: In 2013, some changes in the sleep pattern began in the form of fragmented sleep. Since May 2014, he has presented difficulties in writing with alterations in neatness and size. In addition, he referred to clumsiness for fine motor skills, such as picking for coins in a pocket and a slight resting tremor in the left hand.

Dat-Scan was performed in November 2014, which showed bilateral putaminal hypoperfusion, being worse on the right side. He was diagnosed at this time with Parkinson's disease. In 2015, he lost 5 kg of weight in 6 months. The disease has evolved slowly throughout these years, with progressive clumsiness for both automatic and voluntary movements and muscle

rigidity, especially affecting fine motility. In addition, he has presented progressive difficulty in verbal communication, drooling, and low mood, with a tendency to self-social isolation. In March 2016, he started a low dose of levodopa (100 mg/day) with improvement in sleep and tremor. The dose of levodopa was progressively increased to a current dose of 450 mg/day, associated with opicapone. The patient reports a good motor response to levodopa and no fluctuations in relation to medication, although he reported tiredness/fatigue, especially in the afternoon.

At that moment, he was taking the following medication: rasagiline (1 mg 1-0-0), pramipexole (2,1 mg 1-0-0), levodopa/carbidopa (100/25 mg 1-1-1-1 (intakes at 7-12-17-22-24 h), and opicapone (50 mg 0-0-0-1).

Physical examination: Left-handed. Well-oriented patient, with good cognitive status and no motor or sensory deficits. Mild stiffness of the neck and upper extremities, predominantly on the left. Mild fine motor disability, predominantly on the left side. UPDRS (test performed on March 17, 2022): Mental activity: 1; activities of daily living: 8; motor exploration: 14; Hoehn and Yarh: II; Schwab and England: 70%.

STAT-ON™ objective of use: Given the suspicion of motor fluctuations, a study with STAT-ON™ was proposed. He was asked to wear the sensor for 12 h a day for 7 days and told to press the button on the device after each levodopa intake.

Diagnosis and decision-making: According to the STAT-ON™ record (see Figure 6.1), the patient presented motor fluctuations. A delayed ON was detected in the first levodopa dose in the morning and in sporadic doses, especially in the afternoon. Some dyskinesia was also detected, and it must be indicated that the patient was not aware of it. Some freezing of gait episodes were detected, specifically during OFF or wearing-off periods.

Given the patient's complaint of being suboptimal, with evidence of delayed ON/wearing-off, as reported by the STAT-ON™, an increase in 50 mg of levodopa was indicated at 5 pm. After this adjustment, the patient-reported experiencing a generalized better clinical state.

Discussion: It is well-known that there exists a lack of awareness of most people with Parkinson's disease. This also includes the difficulty in detecting early ON–OFF fluctuations. This data is crucial to adjust the treatment as soon as possible and improve daily quality of life.

Conclusions and take-home messages: The use of STAT-ON™ has been very useful in verifying that this patient has motor fluctuations and making him aware of them, helping to adjust the treatment more precisely.

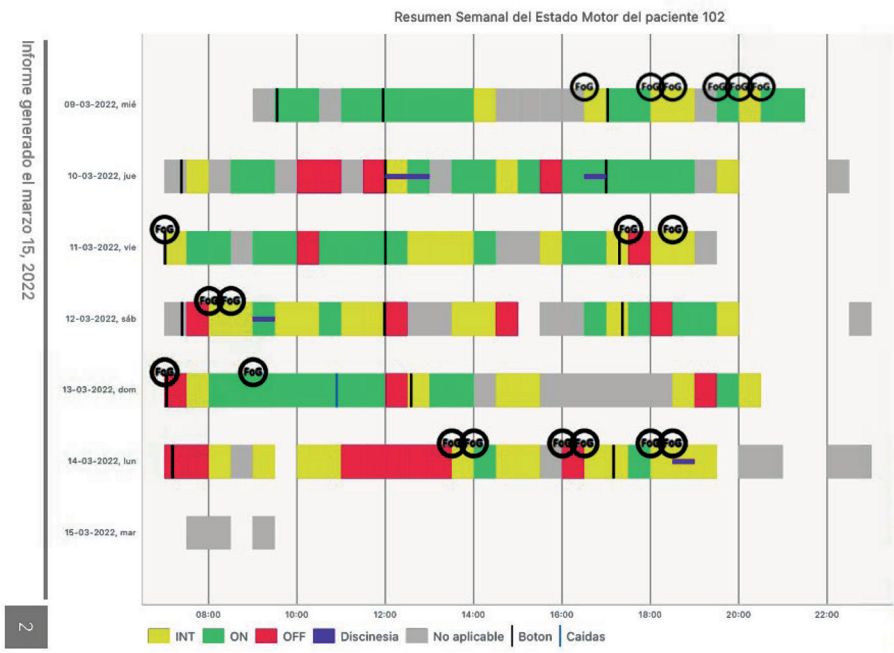

Figure 6.1 Weekly summary reported by STAT-ON™ (it shows delayed-ON in the morning, between 7 and 8 am). Additional OFF periods appeared around 12 am, and later, between 5 and 6 pm were also detected.

6.3 Improving Awareness of the First Motor Fluctuations

Responsible professional: Dr. Anna Planas-Ballvé
Complex Hospitalari Moisès Broggi (movement disorders unit) in Sant Joan Despí. Barcelona.

Personal History: He is a right-handed, Caucasian, 59-year-old man, ex-smoker, working as a telecommunications engineer with a history of mild obstructive sleep apnea.

Parkinson's disease history: His symptoms started at 53 years of age with rest tremor, stiffness, and fine motor clumsiness of the right upper limb, impairing his daily activities and tasks at work. The patient also reported olfactory loss since he was approximately 45 years old. Laboratory workup including complete blood count, renal, liver, and thyroid function was normal. Magnetic resonance imaging of the brain was unremarkable. A diagnosis of clinically established Parkinson's disease was established, according to the International Parkinson and Movement Disorder Society (MDS) task force criteria.

At 54 years of age, treatment with an extended-release form of ropinirole (8 mg/day) optimally controlled the Parkinsonian symptoms. One year after, symptoms were bilateral but markedly asymmetric, and carbidopa/levodopa (75/300 mg) was started with positive control of symptoms.

However, a few months later, safinamide (100 mg/day) was started because the patient explained mild general disability, and dragging of the right leg when walking was observed. In addition, the patient did not notice wearing-off or dyskinesia. At that time, the Hoehn–Yahr (HY) stage was 2, the UPDRS-III score was 10, and the levodopa equivalent daily dose (LEDD) was 590 mg.

STAT-ON objective of use: The use of the device was proposed since the neurologist suspected initial motor fluctuations and with the objective to assess the progression of the first motor fluctuations.

Diagnosis and decision-making: According to the information provided by the sensor, morning akinesia was detected almost every day, and the percentage of daily time in OFF was 4.2%. However, the patient denied having morning akinesia or wearing-off.

Surprisingly, the sensor detected freezing of gait (FoG) in ON, intermediate and OFF states. However, the patient denied suffering from true FoG episodes. Due to the fact that the patient dragged his right leg while walking, it was considered that the device was detecting this motor phenomena of "unilateral dragging gait" (see Figure 6.2)

Due to the results of the first STAT-ON™ report, the carbidopa/levodopa dose was increased (112.5/450 mg), and opicapone (50 mg) was started. In addition, due to bothersome leg edema, dopamine agonists were discontinued gradually.

At 57, the patient began noticing morning akinesia that lasted approximately 15 minutes and wore off motor symptoms in the afternoon. Another STAT-ON™ monitoring period was indicated, with the same HY stage and UPDRS-III as in the first record but higher LEDD (675 mg). The Holter revealed more percentage of daily time in OFF (from 4.2% to 13.6%), with akinesia and wearing-off, especially in the late afternoon (Figure 6.3). On the first day, false positive dyskinesia appeared when traveling by public transport.

Later, at 58 years of age, the patient was even more aware of morning akinesia and wearing-off symptoms and could quite accurately determine the duration of the OFF episodes. The number of levodopa intakes was increased

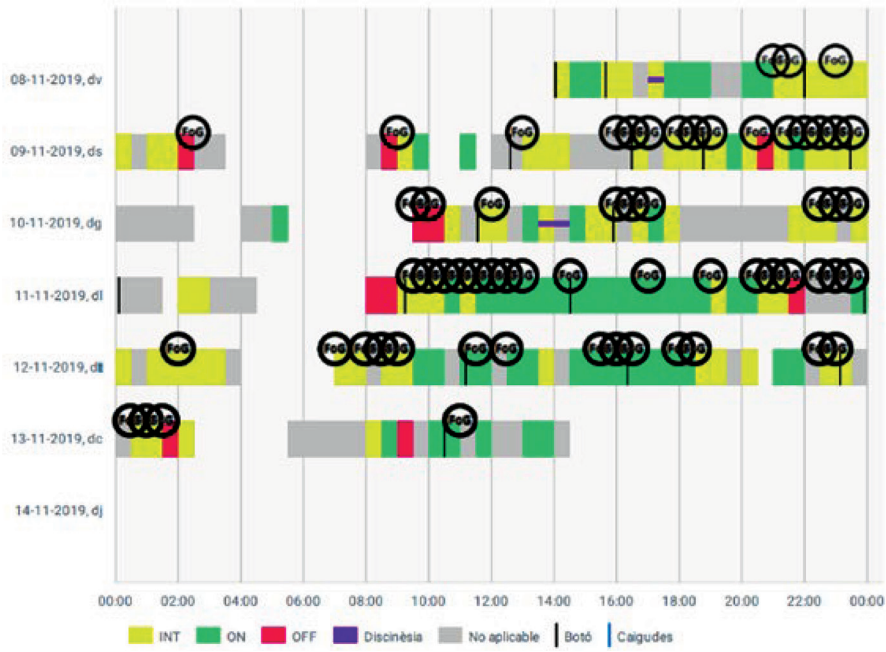

Figure 6.2 First STAT-ON™ report. It shows OFF and intermediate periods in the morning. Intermediate periods are also shown, especially in the afternoon (however, the patient denied having motor fluctuations).

from three to four, and the third STAT-ON™ sensor confirmed the accuracy of the patient quantifying the OFF episodes (Figure 6.4).

Discussion: In this clinical case, STAT-ON™ was very useful since it helped the patient and the neurologist detect early motor fluctuations. The sensor allowed the patient to understand better and to know his symptoms with good accuracy. The presented case is a long supervision period summary (around 3 years), showing different advantages when using this technology (noticing the neurologist the appearance of early, nonreported symptoms by the patient, helping the patient for a better knowledge of his disease and its evolution and promoting a good understanding between the patient and his doctor).

Conclusions and take-home messages: In conclusion, using the STAT-ON™ sensor can increase the awareness of motor fluctuations in patients with PD and help neurologists detect them earlier.

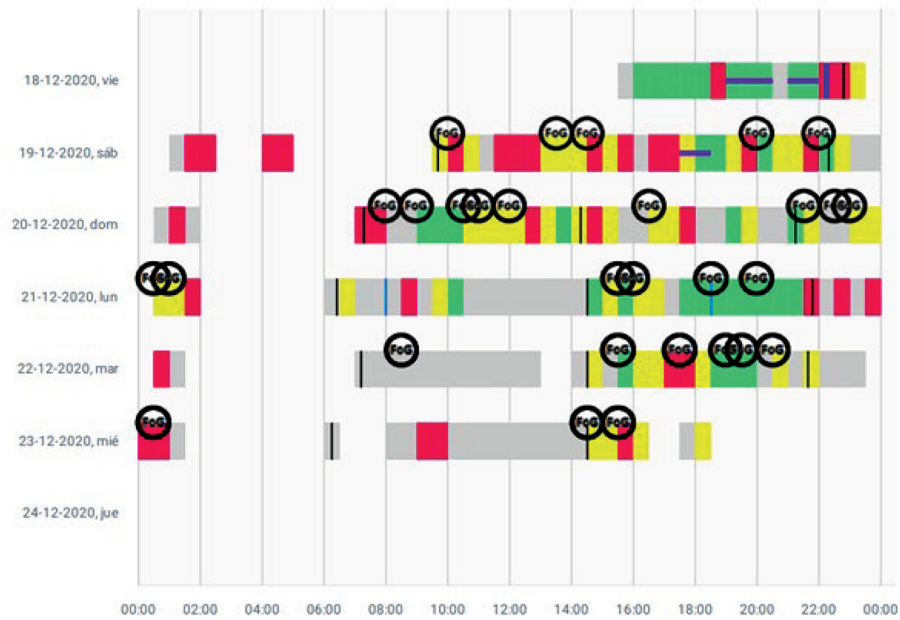

Figure 6.3 Second STAT-ON™ report. The patient is now aware of his morning akinesia and wearing-off episodes. An increase in OFF time and decreased FoG episodes occurred (compared to Figure 6.2).

6.4 Complimenting a Poor Patient's Interview about Her Motor Complications

Responsible professional: Dr. Tània Delgado
Hospital Parc Taulí. Sabadell (Barcelona)

It is about a patient with some problems identifying her motor symptoms correctly, making it very difficult to maintain the necessary interview at the doctor's office during the visit. The patient as the following:

Personal history: 61-year-old woman with an 11-year history of Parkinson's disease. No family history of neurological diseases, with the following personal history: hypertension, vitiligo, right knee prosthesis, and nephrolithiasis.

Parkinson's disease history: In 2011, she attended our clinic due to a recent onset left-hand tremor without other associated symptoms. At physical examination, she had left arm tremor at rest and difficulties with gait without left arm swinging. A cranial MRI was performed, showing a left posterior thalamic chronic microhemorrhage.

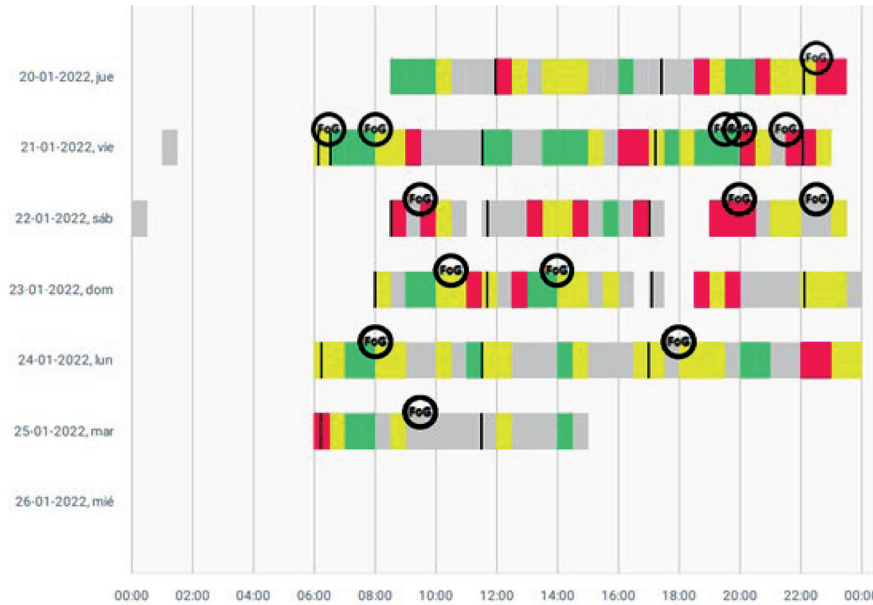

Figure 6.4 Third STAT-ON™ report. In this report, it is shown that FoG is less frequent. However, in this year, the patient complains of having more intense OFF periods.

Parkinson's disease (HY stage 1) was diagnosed, and treatment with rasagiline and pramipexole up to 1.05 mg/day were started, with moderate improvement in tremor.

In the following years, the tremor worsened, and a gait disorder appeared (left leg dragging). Levodopa was started up to 400 mg/day in September 2016 with a good clinical response. She also reported nonprogressive cognitive deficits. No visual hallucinations or delusional ideation were present. A neuropsychological study showed front-subcortical impairment according to Parkinson's disease. In November 2017, she began to have beneficial facial and extremities dyskinesias, and amantadine was added.

From November 2019, she noticed greater difficulties in carrying out her daily activities, and her tremor worsened. As a result, rasagiline was changed to safinamide without a clear benefit.

She did not come regularly for check-ups until January 2021. At that visit the patient reported being worse, but she could only explain that her "tremor" had increased. She used the term "tremor" to refer to tremor and dyskinesias, without being able to quantify it, nor to determine if there was a schedule, or there was a relationship with the medication intake.

At that time, the medication schedule was as follows: safinamide 100 mg (1-0-0), amantadine 100 mg (1-1-0), levodopa-benserazide 150 mg–150 mg-150 mg (at 8 h-15:30 h-23 h), and pramipexole 1.05 mg (1-0-0).

Physical examination: In ON state, she has normal facial expression, no speech problems, no tremor, clumsiness of the hands 2/2/1 bilateral, movements legs one bilateral, no rigidity, no bradykinesia.

It is observed moderate facial, axial and extremity dyskinesias, and dystonic posture in the arms during gait. Gait with normal steps, slightly unstable. Normal postural stability. An HY = 2 was determined, and a UPDRS-III of 13.

STAT-ON objective of use: In this case, it was suspected that the patient had both, dyskinesias and OFF periods. However, the information provided by the patient was very limited and misleading since she confused tremor and dyskinesias.

The objective of using the STAT-ON™ was to determine if there were motor fluctuations and if the called "tremor" episodes were related to OFF periods or dyskinesias, and, subsequently, to allow for optimizing the treatment.

Diagnosis and decision-making: STAT-ON™ was used for 6 days (with a total of 61 h of recording). The total OFF time, during this period, was 12.4 h (20%), an intermediate time of 9.7 h (16%), and an ON time of 17 h (28%) were obtained. The total time with dyskinesias was 4.8 h (8%) (see Figure 6.5 for details and distribution).

In general, she presented intermediate-OFF time from 1 to 5 pm and benefit dyskinesias at 10 am and 6 pm.

Discussion: The results showed that the patient presented OFF episodes at the midday levodopa intake. After the morning and midday levodopa intakes, beneficial dyskinesias were also detected.

Given these measurements, it was decided to lower the total levodopa dose and increase the frequency of doses to 100 mg in four doses (at 8-1-6-11 h). The patient improved clinically, reporting less dyskinesia and sustained response to treatment.

Conclusions and take-home messages: In this case, the STAT-ON™ device provided us with valuable information that could not have been obtained with the interview or the patient's diaries. As the device determines the presence and duration of the OFF periods, as well as dyskinesias, giving an objective perspective of the patient's daily motor status, this information permits the

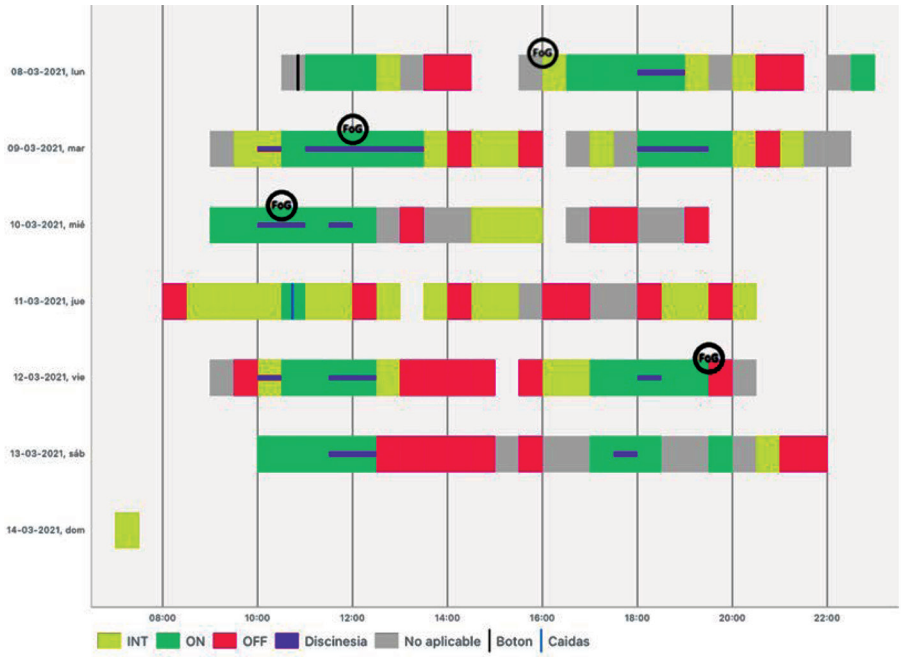

Figure 6.5 The STAT-ON™ report generally shows ON periods with dyskinesias in the morning, followed by OFF period between 1 and 5 pm. Around 6 pm, she experiences ON periods with dyskinesias again.

neurologist the proper adjustment of the treatment, obtaining a good clinical response.

As a final conclusion, it can be said that when the interview with the patients is poor or it is difficult for them to understand how to complete the patient's diaries, the STAT-ON™ device can be a very good alternative, helping the understanding of the patient's motor state.

6.5 Indirect Detection of Probable PD Nonmotor Fluctuations (NMF)

Responsible professional: Dr. Asunción Avila
Complex Hospitalari Moisès Broggi. Sant Joan Despí (Barcelona)

Parkinson's disease history: The patient is a woman. In July 2005, a 67-year-old female was referred to our movement disorders unit for the 1-year duration of nondisabling intermittent resting tremor in her right hand. Her past medical history revealed arterial hypertension.

On neurological examination, the patient had normal cognition. An intermittent mild resting tremor was observed in the right hand, as well as mild signs of cogwheel rigidity and bradykinesia. Gait and balance were normal and postural reflexes (UPDRS-III 11, Hoehn–Yahr 1.5). The diagnosis of idiopathic Parkinson's disease (PD) was entertained. During the first years, the patient had a good and maintained response to treatment with rasagiline 1 mg once daily and ropinirole extended release 8 mg once daily.

Three years after the diagnoses, the treatment was optimized with 300 mg/day of levodopa/benserazide with good clinical benefit. In July 2020, when she was 72, she came urgently to our Unit because she began experiencing an unpleasant feeling of emptiness in her abdomen that appeared in the afternoon, with no relation to the levodopa dose or other drugs. She described her uncomfortable sensation as "*nervousness*," "*if something was missing,*" and "*if I was hungry*." The episodes could last between minutes and hours. The patient said that "*she didn't experience painful sensations*." In addition, she said that "*when it happened to her, she was useless, and she couldn't do anything*." Nevertheless, she denied having motor fluctuations (MF), freezing of gait episodes, or dyskinesias. Over the next 5 months, subsequent trials of modifying treatment were not helpful:

- Increasing the number of levodopa intakes and decreasing their intervals.
- Increasing the total dose daily of levodopa up to 800 mg/day with benserazide in four doses.
- Increasing daily dose of ropinirole extended-release up to 12 mg once daily.
- Adding opicapone 50 mg in a single daily dose.
- Adding entacapone 200 mg with some dose of levodopa.

The patient did not experience improvement with any treatment, and some modifications were abandoned in the first days because she felt worse. At the physical examination, she had mild right-sided parkinsonism with minimum right-hand tremor at rest and bradykinesia (UPDRS-III 5, Hoehn–Yahr 1.5). The psychiatrist of our movement disorders unit evaluated the patient without diagnosing her with any psychiatric pathology suggestive of specific treatment.

STAT-ON™ objective of use: Given the persistence of the symptoms, it was decided to use STAT-ON™ in order to try to identify slight motor fluctuations (MF) that the patient could not identify herself.

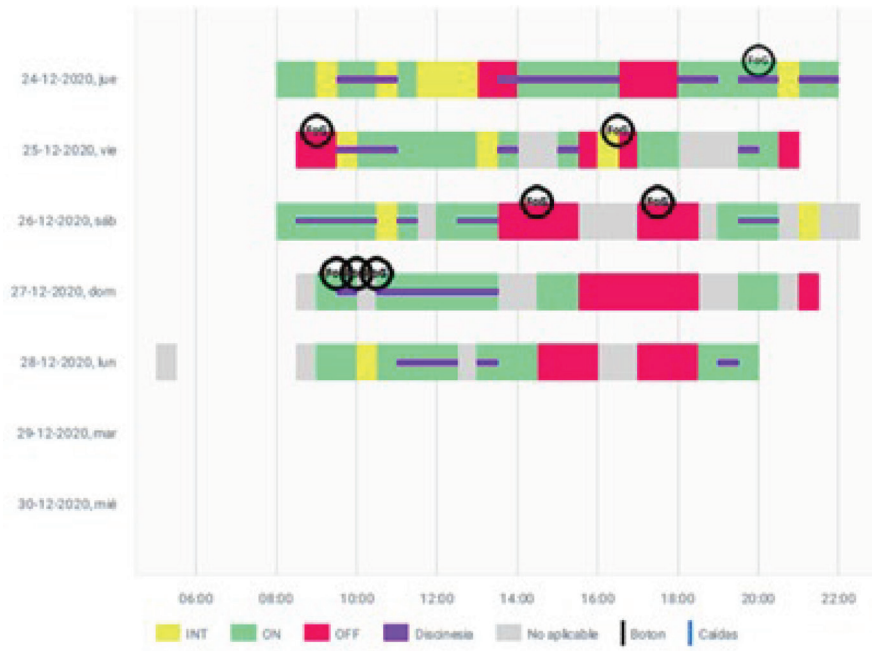

Figure 6.6 STAT-ON™ report showing a predominant OFF period between 2 and 7 pm, in coincidence with the experienced nonmotor fluctuation.

After the use period of 5 days, it was appreciated (Figures 6.6 and 6.7) that the patient presented OFF periods in the afternoon, especially between 2 and 7 pm, which coincided with the uncomfortable abdominal sensations that she had described. The Holter also recorded some isolated freezing of gait (FoG) episodes.

Diagnosis and decision-making: After the detection of the motor fluctuations (MF) that the patient was unable to detect herself, it was considered that, probably, the patient experienced nonmotor fluctuations (NMF) in the form of anxiety, abnormal abdominal sensations, and/or restlessness in coincidence with MF.

The patient was treated with rasagiline (1 mg/day), levodopa/benserazide (200/50 mg) in four doses daily, and ropinirole extended release 12 mg once daily. The patient was informed about the STAT-ON™ results and our suspicion about the coincidence between the MF and NMF periods. Additionally, we decided to substitute rasagiline for 100 mg of safinamide once a day.

After this intervention, the patient significantly improved her probable NMF. Three months later, a new STAT-ON™ registration was made during

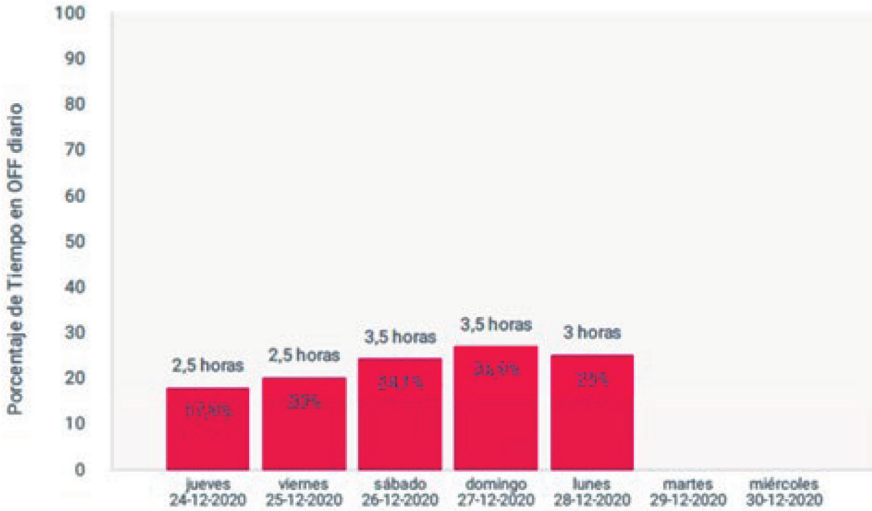

Figure 6.7 Percentage and number of OFF hours per day detected by STAT-ON™ (December 24 to 28, 2020).

3 days, and an evident reduction of the daily OFF time was detected, confirming the correlation between the patient's MF and NMF periods (see Figure 6.8).

Discussion: In Parkinson's disease, nonmotor symptoms can fluctuate (NMF) like motor symptoms (MF) [1]. An NMF can be seen as any change in the severity level of the nonmotor symptoms [1, 2], and many patients with MF also experience NMF with a prevalence in the range from 17% to 100% [2, 3].

This wide variability may be due to the difficulty in the identification of NMF since the diversity of fluctuating nonmotor symptoms, its largely subjective nature, and a frequent lack of perception of NMF despite the high impact of nonmotor symptoms on the autonomy and quality of life of the patient.

Twenty-eight percent of patients who experience both MF and NMF complain that NMF is more disabling than MF [3, 4]—psychiatric nonmotor symptoms related to motor symptoms in their timing and number of ON–OFF switches. The NMF can be present simultaneously with or later than MF [3].

Considering these PD aspects, it can be said that identifying FM using STAT-ON™ can help the neurologist indirectly identify the patients' NMF.

Conclusions and take-home messages:

- NMF include any nonmotor symptom change in the severity level, and their identification is difficult in clinical routine.

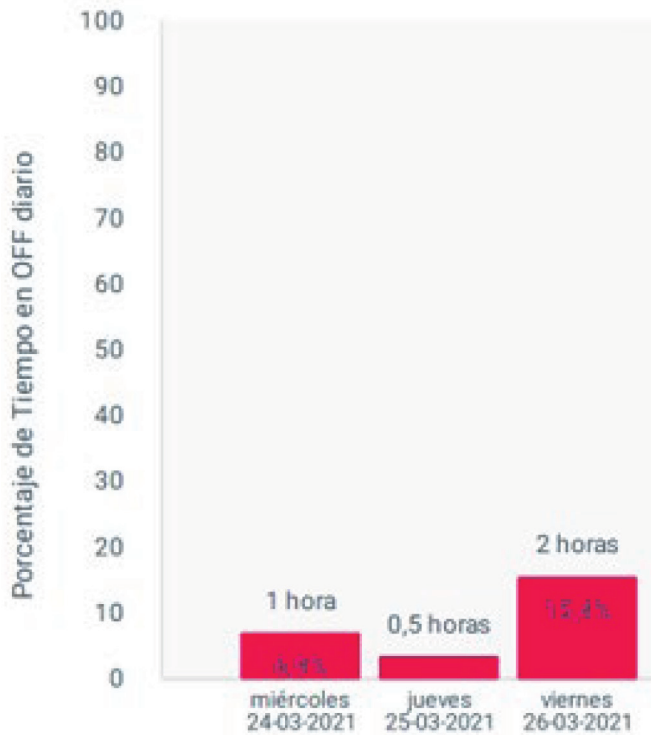

Figure 6.8 Percentage and number of OFF hours per day detected by STAT-ON™ 3 months later (from March 24 to 26, 2021).

- NMF develops simultaneously or after FM, so the identification of FM by STAT-ON™ can help professionals to identify NMF indirectly.

6.6 Deciphering the Patient's Complaints using STAT-ON™

Responsible professionals: Dr. Alexandra Pérez-Soriano and Dr. Núria Caballol
Unitat de Parkinson. Centro Médico TEKNON. Barcelona.

Personal history: A 68-year-old woman attended in 2020. She was diagnosed with PD in 2015. She graduated when she was 22 years old and worked in the bank sector until her retirement when she was 55 years old.

In her personal history, it was only remarkable dyslipidemia and hypothyroidism. Regarding family history, no other members had been diagnosed with PD. However, her mother, grandmother, and two uncles suffered from tremors.

Parkinson's disease history: Regarding premotor symptoms, hyposmia and a possible REM – Behavior Disorder (RBD) and constipation, were present. She had never been diagnosed with depression, although she defined herself "*as an obsessive and anxious person*."

Her PD started with a rest tremor in her right leg and a rest and action tremor in her left arm and left leg. Initially, she was diagnosed with anxiety and received treatment with escitalopram and benzodiazepines for 3 months. Due to the persistency of the tremors, levodopa/carbidopa 300 mg was then started along with pramipexol-immediate release 0.18 mg with a good response. In 2016 she started to have motor fluctuations in the form of delayed-on in the morning, thus safinamide was added. From 2016 to 2020, her symptoms were quite well-controlled with levodopa-carbidopa 300 mg, pramipexol 1.05 mg, and safinamide 100 mg (levodopa equivalent dose of 655 mg/day).

In January 2020, she complained of bothersome movements in her right leg that appeared while standing. She referred to these right-leg movements as "*tremors*," though during her follow-up visit, the movements clinically seemed dyskinesias. She also described that her right foot turned inwards, suggesting dystonic right foot movements associated with pain in her right leg. OFF periods with pain and right foot dystonia were suspected, and opicapone 50 mg was added in June 2020 to the treatment with partial relief.

However, in 2021 she noticed a worsening of her right leg movements that were especially annoying while standing and talking to someone in the street. Due to these symptoms, she avoided going out and stayed at home more than usual. Axial dyskinesia was also seen at the clinical examination hence amantadine 200 mg/day was added to her treatment schedule.

In December 2021, the equivalent levodopa dose was 855 mg/day, and her treatment was as follows: levodopa-carbidopa 100 mg 1-1-1 (300 mg/day), pramipexol 1.05 mg 1-0-0, safinamide 100 mg 1-0-0, opicapone 50 mg 1-0-0, and amantadine 100 mg 1-1-0.

In 2021, when she was asked about "OFF states," she was doubtful at first, saying that "*she wasn't sure she was having any*" but mentioned that she "*may be having 2 or 3 h a day in which she noticed worsening of dexterity in her left arm and leg, and generalized rigidity and slowness of movements*."

Regarding the nonmotor symptoms, she complained of having anxiety and excessive sweating, but not in the OFF state. She was not sure about the amount of dyskinesia per day.

Physical examination: The progression of the UPDRS-III ON over the last years was from a UPDRS-III ON of 9 and an H and Y = 2 in 2019 to a UPDRS-III ON of 19 and a H and Y = 2, in 2021.

At the physical examination in the ON state, left rigidity and left bradykinesia were observed, along with axial and right leg dyskinesia.

In the OFF state, her left bradykinesia and rigidity worsened, and rest tremor was present in her right leg. Freezing of Gait was not observed.

STAT-ON™ objective of use: Although, in the present case, the presence and duration of the motor fluctuations could have been inferred from the clinical interview, the patient still showed many doubts regarding several aspects of her motor symptoms. Therefore, the objectives of using the sensor were:

- To confirm the existence of OFF periods.
- To explore more details about the timing and duration of the OFF periods.
- To confirm if the annoying right leg movements were dyskinesia.
- To analyze the timing and duration of the suspected dyskinesia.

The patient was instructed to wear the sensor for one week. She was trained to press the button at the time of the levodopa dose. At the same time, she was given a simple diary to write down her daily activities, as well as the precise moment in which her right leg movements became "annoying."

Diagnosis and decision-making: The report of the STAT-ON™ was analyzed with the patient. The dyskinesia and OFF periods shown by the report (Figure 6.9) were checked day-by-day along with the patient diary shown in Figure 6.11.

The diary is helpful if the patient collects some activities that could be false positives (going by car or transport, sweeping, etc.). Nonmotor symptoms (anxiety and pain) can also be recorded to check if the nonmotor fluctuation occurs along with the motor OFF state.

We can do a detailed analysis of Figure 6.9 contents:

- She came to our clinic to put the sensor on Friday 10. She arrived at her home at 10 am, and according to the report, she was in the ON state with dyskinesia, although she did not indicate the dyskinesia as bothersome that day in the diary (Figure 6.11). At midday and night, she was in OFF state. In total, 4 h in OFF were detected by the sensor on Friday 10 (Figure 6.9B), which represents 30.8% of her total wake time.
- On the second day (Saturday 11), the patient said she had morning akinesia for 20 minutes. Afterward, she was in an intermediate state, and right leg dyskinesia was detected. In the afternoon, the patient explained

Figure 6.9 (A) Results of the first 3 days. After the morning akinesia period, she had ON with bothersome dyskinesia. (B) Total number of hours in the OFF time distributed per day.

that she was shopping, and although she was walking and active, she was in the OFF period.

- On the third day (Sunday 12), she marked 2 h in which her right leg movements were present and especially annoying: at 1 pm and 10 pm (Figure 6.11). This last dyskinesia period on Sunday 12, just after taking the levodopa dose (Figure 6.9A), could raise the possibility that her dyskinesia could be biphasic. The day before, she also had dyskinesia at 11 am while in the intermediate state.

Overall, in the 3 days analyzed, the OFF periods were present in the morning, midday, and night. The sensor also helped to show that the motor state was worse after midday and that she was better after the first morning levodopa dose, despite the bothersome dyskinesia.

In the report of the next 4 days, a better motor state was generally observed, with less OFF time per day (Figure 6.10):

- On the fourth day (Monday 13), she was doing housekeeping and reading in the morning. In her diary, she marked annoying symptoms at 10 am, 11 am, and 12 am, while doing these activities. (Figure 6.11). The report of the STAT-ON™ device showed a dyskinesia period from 10:15 am to 1:45 pm (Figure 6.10A).
- On the fifth and sixth days of monitoring, the patient marked bothersome dyskinesia on Tuesday 14 at 1 pm, while cooking and at 6 pm while she was shopping. Nonetheless, on that day, the STAT-ON™ did not capture the dyskinesia. Similarly, on Wednesday 15, she went out to a restaurant to have lunch at 2 pm, noticing the supposed annoying dyskinesia again, but the sensor did not detect them.

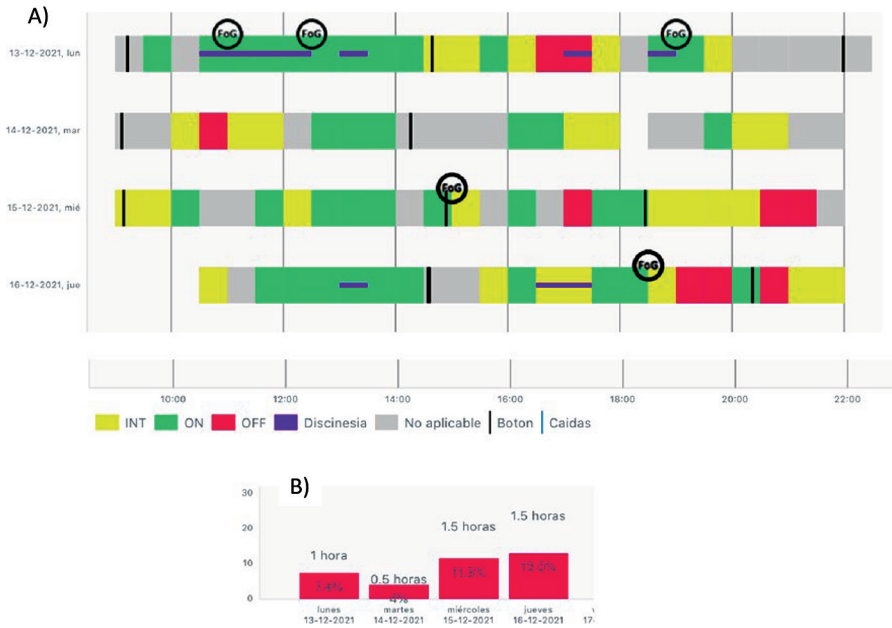

Figure 6.10 Compared with the previous 3-day monitoring period (Figure 6.9), the report shows a better motor state with an average of 1.5 h per day in OFF state.

After wearing the sensor, the patient's awareness of the motor complications improved and the clinical hypothesis of what was happening regarding motor complications was confirmed by the neurologist:

- OFF periods were confirmed. The clinician explained to the patient that during the morning, when she had morning akinesia, and she usually returned to bed to have more rest, she was actually in an OFF state. She also understood that OFF states related to dexterity worsening in her left extremities and slow movement, especially at midday and afternoon.
- Regarding dyskinesia, it was confirmed that they were bothersome most of the time and that they were both peak-dose and biphasic. She was instructed to call them correctly (dyskinesia and not "tremors").

Consequently, the treatment was adjusted. Levodopa total dose was reduced, and levodopa doses were fragmented into five doses: levodopa-carbidopa (five doses of 50–250 mg/day), pramipexole 1.05 mg (1-0-0), safinamide 100 mg (1-0-0), opicapone 50 mg (1-0-0), and amantadine 100 mg (1-1-0).

The dyskinesia improved during 6 months. However, the OFF periods intensity worsened in the next appointments, and an impulse control disorder

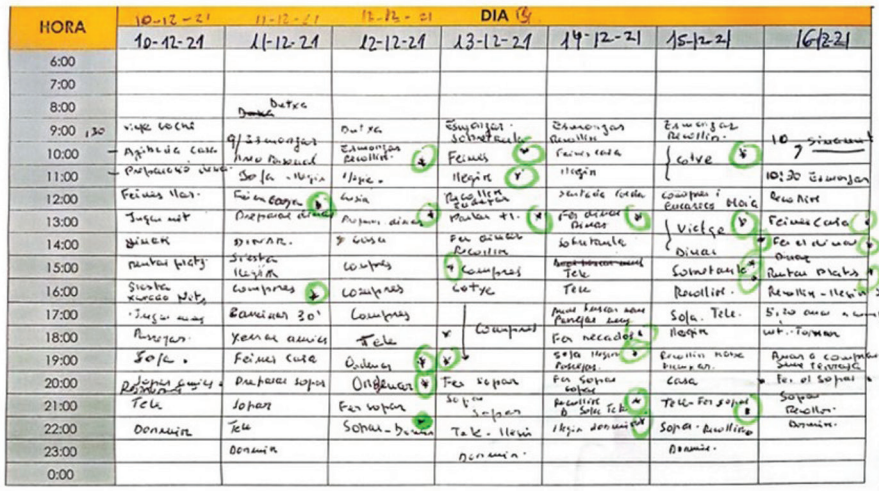

Figure 6.11 Patient's diary while using the sensor. In this case, the diary was useful for the patient to identify bothersome dyskinesia. The asterisks in green represented the moment the patient did not feel good, and the symptoms were bothersome to her. For example, the dyskinesia was annoying on Saturday 11, at midnight, or on Sunday 12, around 1 pm.

appeared (binge-eating). For these reasons, the patient is now being evaluated for deep brain stimulation (DBS).

Discussion: The identification of PD motor complications, in the daily-clinical practice, can be quite well recognized in a thorough clinical interview using the appropriate clinical scales and the Hauser diaries [5–7]. However, while for some patients, the motor symptoms and the motor fluctuations are easily recognized by using these methods, for some other patients, these symptoms cannot be easily identified.

In these cases, the clinical interview becomes more arduous, affecting the capacity of the neurologist to adjust treatment adequately. In addition, these patients are usually not deemed good candidates for clinical trials due to difficulties recognizing symptoms and completing Hauser's diaries. In this context, wearable sensors such STAT-ON™ can be useful to objectively assess motor fluctuations as well as to educate and empower the patient, improving self-awareness to detect motor symptoms and motor complications [8]. Moreover, in an outpatient setting, clinical scales and Hauser's diaries are not always used for reasons of time. Therefore, using the STAT-ON™ sensor can be a "novel way" to objectively assess the motor state of the patient during the day in a real-life scenario.

In the current case, the sensor detected motor complications that the neurologist had already suspected during the clinical interview. In general, the patient knew that sometimes she had OFF states affecting dexterity in her left extremities, and even though sometimes she named the right leg movements as "tremors," dyskinetic right leg movements were observed and suspected by the clinician. However, the use of the STAT-ON™ helped both the patient and the neurologist to increase the degree of self-awareness and better understand the main times when the symptoms became especially bothersome.

The sensitivity and specificity of the STAT-ON™ sensor for detecting dyskinesia are 95% and 93%, respectively, for strong or mild trunk dyskinesia [9]. The sensitivity is lower (39%) for mild limb dyskinesia. Despite these limitations, in our case, the STAT-ON™ report clearly showed the ON dyskinesia periods and only missed mild dyskinesia that the patient referred to when she was out shopping or eating. This indicates that the bothersome dyskinesia was not necessarily more intense but made them bothersome because they were present when she was doing activities in which she was in public or concentrating at home (reading and cooking).

Conclusions and take-home messages: In addition to the very good characteristics of STAT-ON™, identifying and analyzing the motor symptoms related to PD, it is convenient to emphasize that:

- It enables the precise identification of when a certain symptom (dyskinesia or OFF) is bothersome or disabling.
- It can be a very useful tool to educate the patient regarding suffering motor complications. For example, in the presented case, before wearing the sensor, the patient sometimes referred to the dyskinesias as "tremors" and after wearing the sensor, the patient recognized her dyskinesias better.
- For the neurologist, STAT-ON™ offers the possibility to better understand the patient's complaints and adjust the dopaminergic treatment.

6.7 Ambulatory Monitorization of a Patient with Advanced PD

Responsible professional: Dr. López-Ariztegui Núria
Movement Disorders Unit of the Hospital Universitario de Toledo. Toledo.

Personal history: The patient is a 70-year-old female, in follow-up at the movement disorders unit since she was 58 years old for PD and poor motor

control in recent years. There is no remarkable personal history except for hypercholesterolemia, surgery for hallux valgus and saphenectomy, and family history of PD in several paternal relatives.

Parkinson's disease history: In 2010, at the age of 58, she consulted for several months of rest and postural tremor in the left arm, and loss of agility as well as hyposmia. She presented left asymmetric rigid-akinetic-tremor syndrome on examination with UPDRS-II = 3 and -III = 12.

The following complementary tests were carried out:

- DaTSCAN ioflupano (123I): hypo uptake of both putamens, asymmetric with greater right involvement.
- Cerebral MRI: within normality.
- Laboratory tests with biochemistry, complete blood count, copper, and ceruloplasmin: within normality.
- Genetic analysis: heterozygous variant gly2019Ser of the LRRK2 gene.

With the diagnosis of PD Hoehn and Yahr stage I, a treatment with rasagiline was started. After 6 months, the transdermal rotigotine was added up to 12 mg daily, with clinical improvement in tremor and daily life activities (DLA).

In 2013, she reported worsening of mobility with left leg dystonic and difficulties in DLA and sports such as swimming. Levodopa/carbidopa (LD/CD) was added up to 300 mg in three doses with significant motor improvement. She remained stable for 2 years, and in 2015, she started with morning akinesia and fragmentation insomnia due to nocturnal akinesia. An uncontrollable behavior compatible with impulse control disorder (ICD) in the form of kleptomania emerged. Since the ICD provoked marked anxiety, the dose of rotigotine was reduced to 8 mg, and the dose of LD was increased to four doses of 100 mg daily, with improvement in the ICD.

In the following years, she continued with motor fluctuations, mainly nocturnal and morning akinesia and mild wearing-off, and she maintained independence in DLA, although she had to give up swimming.

She referred mild and nondisruptive choreic dyskinesias. Different treatment adjustments were made, fragmenting LD/CD, adding opicapone, and an attempt to change from rasagiline to safinamide, but she did not tolerate it due to adverse events (AE). Lastly, second-line therapies (SLT) were proposed, but patient and relatives were reluctant to do all of them since, with medication adjustments, she felt relatively well.

From the very beginning, she had been diagnosed with anxious depressive symptoms controlled by psychiatry with escitalopram and bromazepam.

Over time, nonmotor symptoms (NMS) appeared: low back pain related to lumboarthrosis that worsened in the afternoon, hypertension in off episodes that require various antihypertensive medication adjustments, episodes of excessive sweating, nocturia, constipation, mood, and fluctuating sleep with the need for antidepressant treatment adjustments.

In evaluation after the COVID pandemic, the patient was worse; she continued the treatment with rasagiline 1 mg, rotigotine transdermal 8 mg LD/CD 800 mg in five daily doses, and opicapone 50 at night (LEDD 1540 mg): she spent the afternoon sitting without activity because she was tired with lower back pain.

She had morning akinesia lasting an hour and disruptive wearing-off around 1 pm that interfered with her DLA. Since she was still reluctant to SLT, ambulatory monitoring with STAT-ON™ was scheduled to characterize the OFF episodes.

Physical examination: MDS-UPDRS-III-Off state = 42. It was observed left asymmetric rigid-akinetic tremor syndrome with slow but autonomous gait and freezing of gait (FoG) at the beginning of walking and when turning.

MDS-UPDRS-III-On state = 9, with mild hypophonia, postural alteration with Pisa to the left, minimal asymmetry in bilateral tapping maneuvers with mild axial choreic dyskinesias and left leg, without tremor.

MDS-UPDRS-I 0 = 9 (mood and anxiety, fatigue, sleep, pain, constipation, urinary), II = 10, IV = 6. The Hoehn and Yahr state is 2 in ON, 3 in OFF state.

STAT-ON™ objective of use: The patient was diagnosed with familial PD concerning heterozygous mutation gly2019Ser of the LRRK2 gene. A complicated PD stage is observed with motor and nonmotor fluctuations and dyskinesias, susceptible to SLT.

Although the presence of disruptive motor fluctuations was clear from history, the patient and family underestimated them. They related them with fatigue and did not decide on any SLT solution. It was proposed to carry out ambulatory monitoring with STAT-ON™ to quantify and characterize her OFF moments and achieve adjustment and adherence to new therapeutic measures. The patient was instructed to press the event button with each LD/CD intake.

Diagnosis and decision-making: The STAT-ON™ report covered 6 days (Figures 6.12 and 6.13) and showed an active patient who walked an average of 18,000 steps per day, but she was less than 50% of the monitored time in

Días monitorizados:	6
Tiempo monitorizado:	83.5 horas
Nº episodios FoG:	63
Media episodios FoG/día:	10.5±8.4
Media minutos andando/día:	183.8±67.4
Media número de pasos/día:	18041.5±6699.3
Tiempo total sin diagnóstico (% tiempo monitorizado):	6 horas (7.2%)
Tiempo total en OFF (% tiempo monitorizado):	17.5 horas (21.0%)
Tiempo total en Intermedio (% tiempo monitorizado):	20.5 horas (24.6%)
Tiempo total en ON (% tiempo monitorizado):	39.5 horas (47.3%)
Tiempo total con discinesias (% tiempo monitorizado):	11 horas (13.2%)
Umbral personalizado de bradicinesia (Fluidez de zancada) >8 óptimo <6 subóptimo	6.6±0.5

Figure 6.12 Summary of STAT-ON™ report. As indicated, it was detected a 21% of OFF Time, a 47.3% of ON time, and a 24.6 % of intermediate state. She was suffering from dyskinesias during a 13.2% of the monitoring time.

ON state. She spent 21% of the time in the OFF state and 24.6% in the intermediate state with the following distribution:

- Morning akinesia, with episodes of FoG, and a latency in the effect of the first dose of more than 30 minutes.
- Episodes of wearing-off in the rest of the LD/CD doses, with a variable duration of 30–120 minutes with a transition between intermediate and OFF state, associated with FoG phenomena less frequently than in the morning.
- Dyskinesias generally appeared in the afternoon but accounted for only 13% of the monitored time, and the patient reported them as not disruptive.

After discussing these results with the patient, it was decided to perform an apomorphine test, which was positive at the dose of 4 mg without adverse effects. Treatment was adjusted by increasing the dose of LD in the first and second levodopa intakes up to 200 mg. Subcutaneous apomorphine injections were started for OFF periods rescue. In the subsequent visit, the patient explained that she recognized well the OFF episodes, and that she only used the apomorphine midday rescue, if she had to go out to do some activity.

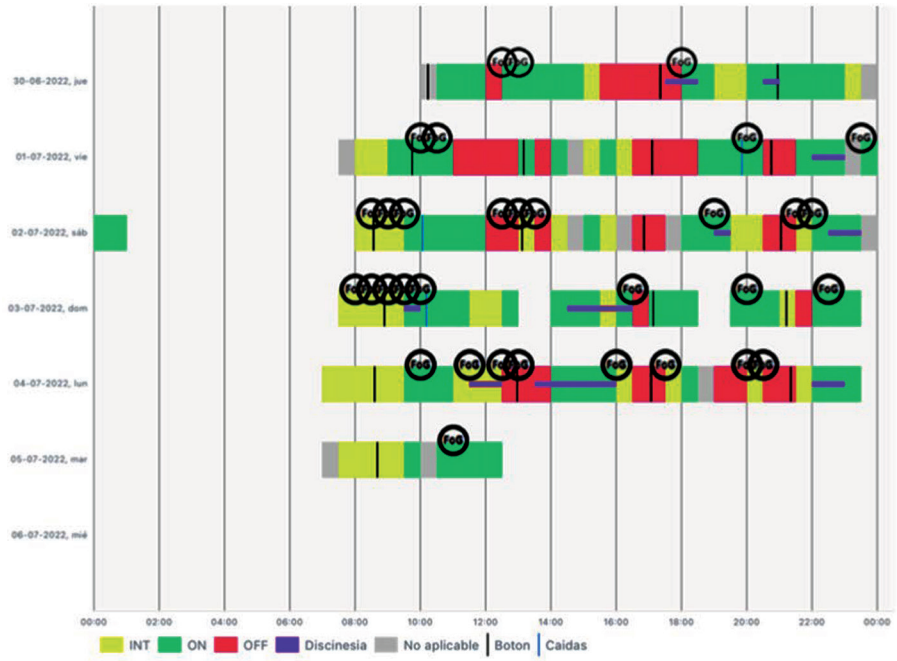

Figure 6.13 The STAT-ON™ report shows intermediate state in the morning with FoG episodes. The report demonstrates OFF states associated with the LD/CD doses. Dyskinesias were especially present in the afternoon.

Discussion: This case reflects a common problem found in the clinical practice with patients with PD: the difficulty for many patients and their relatives to recognize the OFF symptoms [1]. Recognizing OFF time can be especially difficult when nonmotor symptoms such as fatigue, pain, or mood disorders dominate the OFF periods. In these cases, when performing ambulatory monitoring and reviewing it with the patient, they can realize that their symptoms are related to LD doses and help them to have greater therapeutic adherence.

A second common problem, in clinical practice, is that the patient and their relatives do not understand the need to change the therapeutic strategy with the transition from a conventional one to an SLT [2]. Sharing with the patient the STAT-ON™ report and showing them in the registry the changes that occur during the day, can help in deciding to move to an SLT or a device-aided therapy.

Conclusions and take-home messages: The use of devices for ambulatory monitoring of PD patients, such as STAT-ON™, helps the physician to know the real motor state of these patients in their daily life. Moreover, it is of great

help for the patient to realize why they do not feel well at a precise moment of the day and, to establish a relationship with medication. Thus, they can understand the different therapeutic decisions that must be made to improve their clinical situation and quality of life, such as the initiation of the SLT.

6.8 Improvement of the Patient's Awareness of the Advanced PD Stage and the Need for a Second-line Treatment

Responsible professional: Dr. Sònia Escalante
Hospital Verge de la Cinta. Tortosa (Tarragona).

Personal history: A 73 years old female with a 15-years history of Parkinson's disease. Some additional data are: treated hepatitis C virus infection, with undetectable viral load, depression and anxiety**.** Previous surgeries: appendectomy, bilateral knee prosthesis, hallux valgus. No family history of Parkinson's disease.

Parkinson's disease history: When she was 58, she was diagnosed with PD. Her initial symptoms were left arm rest tremor and bradykinesia with good response to pramipexole and rasagiline. She had no balance impairment, constipation, or smell loss. She also was diagnosed with sleep disorder, suggestive of REM sleep behavior disorder (RSBD), with good response to clonazepam.

She had a brain MRI that showed leukoaraiosis and a DaTSCAN with a significant reduction of right putamen's dopaminergic activity.

Five years after the diagnosis, the tremor was bilateral, and she started with visual hallucinations and eating behavior disorder. This was controlled by reducing the dosage of dopaminergic agonist agents and starting low doses of levodopa.

When she was 69, she developed motor fluctuations (morning akinesia and wearing-off), needing an extra dose of levodopa. Meanwhile, she showed symptoms of cognitive decline.

At the age of 71, she had morning akinesia lasting 1 h, and nondisrupting dyskinesia appeared. She needed to take 5 levodopa doses, but some were not effective.

At this point, we discussed with the patient the second-line treatment options. She did not meet the DBS criteria because of her cognitive impairment, and apomorphine was not considered a suitable option because of her eating behavior disorder. We explained to her the intestinal levodopa infusion therapy, but the patient was scared and claimed that "*she had good days and*

Figure 6.14 STAT-ON™ summary report showing the above-mentioned situation.

bad days." Hauser's diary was not helpful because she checked 2 items at the same time (OFF and dyskinesias, for example) multiple times.

At that time, the treatment schedule was: rasagiline 1 mg, pramipexole 1.05 mg, levodopa/carbidopa 150 mg five times daily, clonazepam 0.5 mg at night.

Physical examination: In OFF: H and Y = 2.5, UPDRS-III: 29. Occasional Freezing. She needed help with some daily life activities. In ON: H and Y = 2, UPDRS-III: 12. Nondisrupting dyskinesia. Independent for all daily life activities.

STAT-ON objective of use: It was decided to use the STAT-ON™ Holter to record objective data and show them to the patient to make her aware of her real situation. The second foreseen objective was to see if this could help her to decide about a second-line treatment.

Diagnosis and decision-making: The STAT-ON™ device was used for 5 days with a total of 66 h of recordings (see Figures 6.14 and 6.15) with the following conclusions:

- Motor fluctuations were detected: wearing-off, morning akinesia, and nondisrupting dyskinesia.

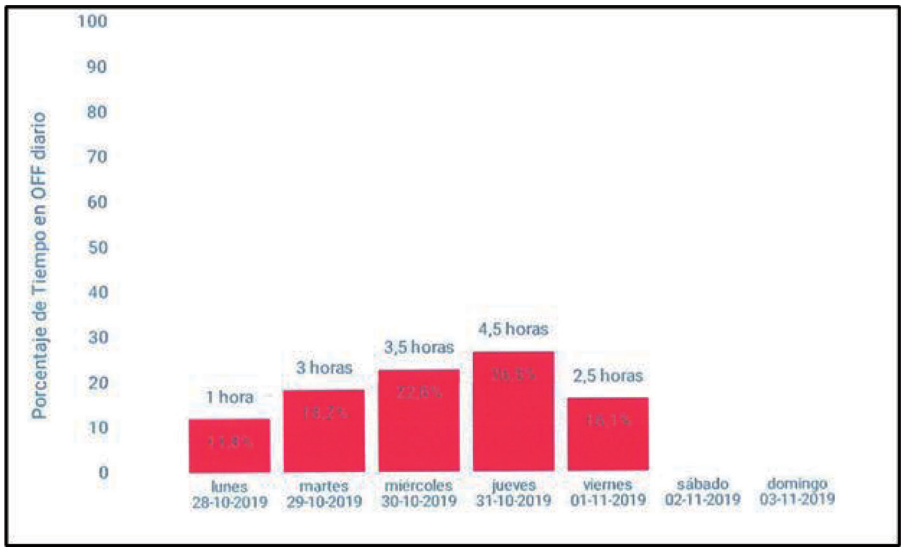

Figure 6.15 Percentage of daily OFF time.

- The total OFF time was 6.9 h (10.4%), the intermediate time was 5.1 h (7.7%), and the ON time was 16.3 h (24.7%).
- The total time with dyskinesia was 9.7 h (14.7%).
- No FoG episodes were detected during the ON periods, and she had dyskinesia almost all the time during ON periods.
- Nearly every day, she had more than 2.5 h of OFF periods, arriving, some days, to 4.5 h.

Discussion: Results obtained from the use of STAT-ON™ were very useful to show to the patient how complicated it was to manage her disease with only oral medications. She was aware of the presence of dyskinesia during almost all the duration of the ON periods and this limited further up-titration of levodopa.

This helped her to understand how frequent her OFF periods were and the difficulty of controlling her disease with only an oral medication approach. She is now treated with levodopa-carbidopa intestinal gel infusion, and the motor fluctuations are now much more well-controlled.

Conclusions and take-home messages: STAT-ON™ device provides objective information, which is extremely useful to optimize dopaminergic treatment, mainly when the information provided by the patient is not clear

enough or when the neurologist suspects that the patients could be minimizing their symptoms,

In patients with advanced-stage PD, who might have problems in identifying ON–OFF periods, this device could be a valuable tool to detect candidates to a second-line treatment.

6.9 Identification of CANDIDATES to a Device-aided Therapy

Responsible professional: Dr. Diego Santos-García
CHUAC – Complejo Hospitalario Universitario de A Coruña. A Coruña.

Personal history: A 58-year-old right-handed woman was referred for PD evaluation. She presented:

- Idiopathic PD with the onset of symptoms 6 years before the visit.
- Previous treatment for pulmonary tuberculosis.
- Plaque psoriasis and psoriatic onychopathy are in remission.
- No known drug allergies.
- No cardiovascular risk factors.
- No toxic habits.
- Chronic constipation.

The treatment was: Sinemet Plus® 1-1-1-1-1 (at 8:45-11:45-14:45-17:45-20:45), Sinemet Retard® (1 pill at night), Ongentys®, Rivotril® (0.5 mg at night), Metoject®, folic acid. Daily dose of levodopa 700 mg/day. Levodopa equivalent daily dose (LEDD) is 975 mg/day. The patient had been treated before with safinamide and dopamine agonists (rotigotine and pramipexol) with no tolerability.

She was retired, living with her sister (principal caregiver), and having good family support. Concerning the familiar history: no cases of PD or any other neurological condition in her family.

Parkinson's disease history: In 2014, the patient started with a resting tremor in her right leg. She received some drugs without good tolerability: Artane® (dry mouth); Neupro® (nausea and vomiting); Mirapexin® (dizziness and constipation). In August 2018, L-dopa was increased, up to 400 mg/day. In October 2020, she started with motor fluctuations, and Xadago® (50 mg/day) was added to levodopa, but it was withdrawn due to dizziness and psoriasis

outbreak. After this, she started with entacapone, and some months after this, it was changed to opicapone with very slight benefit.

The patient was referred to the CHUAC – movement disorders unit for evaluation and consideration about a possible device-aided therapy.

At that moment of evaluation (November 2020), the patient presented with predictable (morning akinesia; wearing-off) and unpredictable motor fluctuations (delayed-ON; no-ON; partial-ON) as well as dyskinesia, sometimes disabling for the patient (especially in mouth when she was in public with other people). During the OFF episodes, the patient developed tremor, rigidity, bradykinesia, anxiety, and sometimes fatigue with a bad mood.

A variability was observed depending on the days, with some days with fewer than 2 h of OFF time during the waking day and others with more than 4 h. In some moments, she felt fatigue and a worse mood with lack of motivation but without being especially worse in her movements.

Complementary tests:

- Cranial and cervical MRI (2018): without significant alterations.
- DaTSCAN (2018): bilateral striatal dopaminergic denervation with left side predominance.

Diagnosis:

- Parkinson's disease of about 6 years of disease duration (from symptoms onset).
- Motor fluctuations and disabling dyskinesia. Very good response to levodopa (Hoehn and Yahr = 2 and UPDRS-III 11 during the ON state).
- Minor depression, mild anxiety, constipation, urinary symptoms, fatigue, and REM sleep disorder as the most relevant NMS. Nonmotor fluctuations (fatigue, mood, and motivation).

Physical examination: The general and neurological examination was done without alterations

Motor assessment:

- UPDRS-IV: 8. OFF time 26-50%. Dyskinesia 1-25%.
- FoG-Q: 5. No significant freezing of gait (FoG) episodes.
- UPDRS-III-OFF (9:10): 35. Language 0. Hypomimia 1. Tremor 6 (0103110). Rigidity 4 (01111). Bradykinesia 16 (32212132). Posture 1. Gait 2. Postural reflexes 1. Global bradykinesia 4. Hoehn and Yahr 2.5.

- UPDRS-III-ON (10:20): 11. Language 0. Hypomimia 0. Tremor 1. Rigidity 1. Bradykinesia 9. Hoehn and Yahr 2.

Nonmotor assessment:

- PD-CRS: 100 (fronto-subcortical 71, cortical-posterior 29).
- NMSS: 47/360 (cardiovascular 0/24; sleep/fatigue 9/48; mood/apathy 7/72; perceptual problems 0/72; attention/memory 1/36; gastrointestinal tract 9/36; urinary symptoms 8/36; sexual dysfunction 1/24; pain and miscellaneous 12/48).
- BDI-II: 8/63. Positive for minor depression.
- QUIP-RS: 0. No impulse control disorder.
- PDSS: 144/150.

Quality of life and autonomy for activities of daily living:

- PDQ-39SI: 32/156 (mobility 19/40; activities of daily living 4/24; emotional well-being 5/24; stigma 0/16; social support 0/12; cognition 1/16; communication 0/12; bodily discomfort 3/12).
- PQ-10: 6/10.
- EUROHIS-QOL8: 27/40.
- ADLS: 60% (OFF); 90% (ON).

STAT-ON objective of use: The patient rejected the option of starting with device-aided therapy. Since the patient had not previously tolerated treatment with dopamine agonists and she did not want to consider deep brain stimulation, a levodopa/carbidopa infusion was proposed. Still, the patient refused the levodopa/carbidopa infusion therapy. Previously, many levodopa adjustments had been conducted without good response, partly due to the development of dyskinesia. Therefore, amantadine was added to her treatment. However, after some months with amantadine the patient stopped due to no tolerability (she felt impairment in movements).

To know the daily OFF time during the waking day, the STAT-ON™ Holter was used for 1 week in May 2021.

Diagnosis and decision-making: A clear pattern was detected from the report generated, and two different OFF periods throughout the day were identified. Firstly, in the morning (from 8 to 10 am) and then after midday (from 2 to 4 pm) (see Figure 6.16).

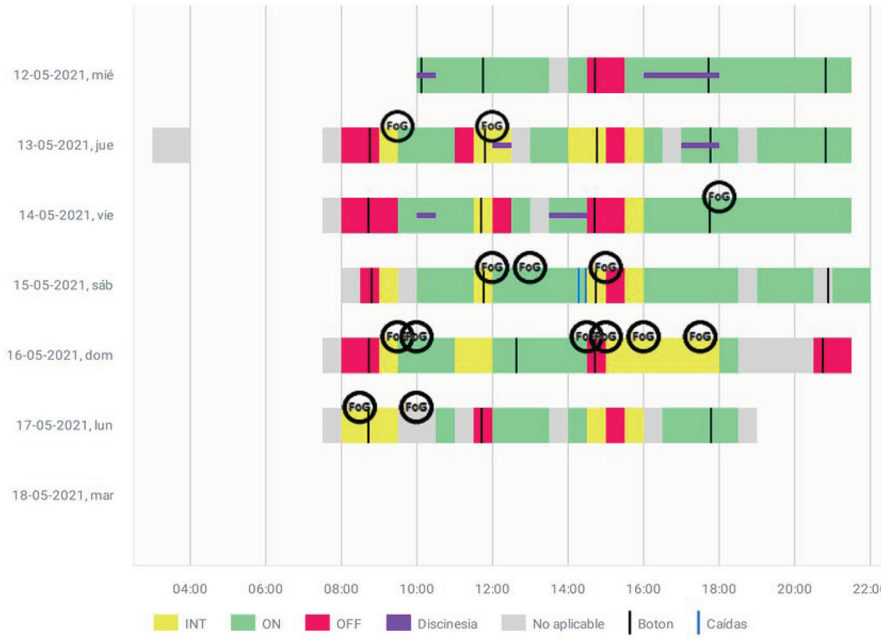

Figure 6.16 STAT-ON™ report summary showing well-defined OFF time periods in the morning and after midday. Many FoG episodes were also detected.

Moreover, a third moment of OFF time, though shorter, was detected around 12. PM. However, the status of the patient during the evening, in general, was better, with quiet ON time.

The patient was ordered to press the button at the time of taking levodopa, to find out the relationship between the episodes with these moments. The information collected was consistent with morning akinesia and wearing-off at the second and at third doses of levodopa during the day. Fewer time with dyskinesia was also detected. Interestingly, 14 FoG episodes were also captured. Only very few of the FoG episodes were during the ON time, whereas the rest of the FoG episodes were during the OFF time or intermediate state.

Although previously, the patient was asked about FoG episodes and answered that she did not having this symptom, after checking the monitoring records, she commented that very brief minor episodes could have appeared sometimes when she felt worse.

The patient's perception of presenting more FoG episodes as per what was recorded by the STAT-ON™, especially on Sunday 16 (Figure 6.17).

Daily OFF time ranged from 1 to 3 h (see Figure 6.18). After reviewing the monitoring record with the patient, she perfectly saw the presence of fluctuations throughout the day, and she agreed to start with levodopa/carbidopa

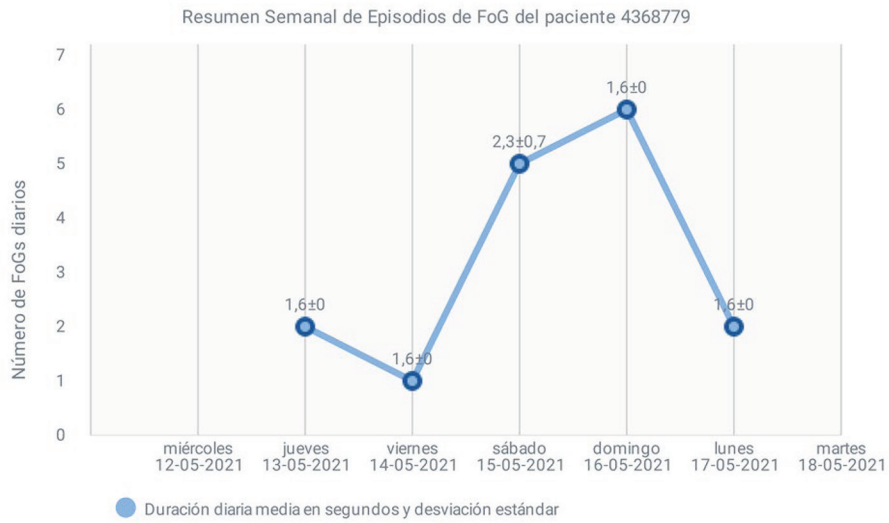

Figure 6.17 Weekly FoG report showing that the worst day regarding the number of FoG episodes was on Monday 16.

infusion therapy. The patient was treated with Duodopa® in May 2021, with a very good response and tolerability.

Discussion: The present case is one example of the possible utility of the STAT-ON™ as a tool to identify a patient with advanced PD as a candidate for device-aided therapy.

This patient was a 5-2-1 criteria positive patient [12] with motor fluctuations, nonmotor fluctuations, and dyskinesia. According to the CDEPA criteria, this patient was an advanced PD patient [13]. A recent publication about the opinion of expert neurologists on PD using the STAT-ON™ showed that the STAT-ON™ could be a useful tool to detect advanced PD [14].

Interestingly, the monitoring record about the patient's state during the waking day obtained with the STAT-ON™ was useful for informing the patient and changing the decision about the therapy. Although she rejected initially to start with a device-aided therapy, after reviewing the STAT-ON™ results, she agreed to start with levodopa/carbidopa infusion therapy. Moreover, the STAT-ON™ made it possible to identify the presence of FoG episodes, which have not been previously detected with the clinical evaluation. The STAT-ON™ has also been validated with advanced-stage PD patients with levodopa-carbidopa intestinal gel or deep brain stimulation [15, 16]. Although it was not done, the STAT-ON™ could have been used for monitoring this patient's response to Duodopa® in this patient both in the short and long term.

Figure 6.18 Weekly summary of OFF time.

Conclusions and take-home messages:

- STAT-ON™ was used in a patient with advanced PD with motor fluctuations and dyskinesia who rejected to start with a device-aided therapy.
- The type of motor fluctuations and OFF time was perfectly identified. FoG episodes were detected when they had not been previously identified with the clinical assessment.
- The information collected with the STAT-ON™ was useful for objectively showing the patient some complications of her disease (OFF episodes, dyskinesia, and FoG) and convincing her of the decision to start with a device-aided therapy.
- A correlation between motor OFF episodes and some NMS (fatigue and bad mood) was collected.

Finally, the patient was treated with levodopa/carbidopa infusion, and her symptoms improved.

6.10 STAT-ON™ Use for LCIG Tube Adjustment

Responsible professional: Dr. Jaime Herreros Rodriguez
Hospital Universitario Infanta Leonor (Neurology Department). Madrid.

Personal history: 73-year-old male with an excellent physical condition and cognitively intact. His personal history was unremarkable except for arterial hypertension treated with enalapril/hydrochlorothiazide (20/12.5 mg).

Parkinson's disease history: He was followed in the clinic for advanced Parkinson's disease (PD) (stage III of H–Y) with motor complications (wearing-off, no-on, and occasional ON–OFF phenomena). He was diagnosed with PD at the age of 65, and a good response to ropinirole (started in 2014) was obtained. After 2 years, levodopa was added with good clinical benefits. Opicapone was added in 2019, and safinamide in 2020.

Treatment: safinamide (100 mg at dinner), opicapone (50 mg at breakfast), Levodopa/carbidopa 250 mg 1.5 (8 am)-1.5 (1.30 pm)-1/2(6 pm)-1/2 (9 pm), ropinirole extended-release (8 mg at breakfast).

Due to poor medical control despite oral pharmacological optimization, it was decided to start with levodopa-carbidopa intestinal gel in continuous infusion (LCIG) in October 2021 (Duodopa: morning dose (18 mL); continuous dose (3.2 mL/h); extra dose (2 mL)).

After 2 weeks of starting the LCIG, the patient reported a significant improvement in his daily activities and motor state. The motor state was recorded using the STAT-ON™ device.

However, 2 weeks later, the patient-reported acute motor impairment without achieving a good clinical motor situation up to 6 h after starting the daily infusion of levodopa.

Some decisions were made: the morning dose of LCGI was increased to 22 mL, an abdominal X-ray was requested to check the position of the LCIG tube (Figure 6.19, left), and it was prescribed a new use of the STAT-ON™ device to analyze the patient's motor state along the day.

STAT-ON™ objective of use: Considering the characteristics of the STAT-ON™ device, it was recommended its use in the present case to demonstrate the clinical worsening 2 weeks after LGCI was instituted (LCIG treatment with and without normal functioning). Results in Table 6.1 show the opinion and feeling of the patient at the beginning (2 weeks after the LCGI adjustment) and when the mispositioning of the tube was detected.

Diagnosis and decision-making: After confirming the LCIG tube mispositioning in the stomach, starting with prokinetics (domperidone three times daily) was decided. The patient recovered his good previous clinical situation (functional and motor) five days later. An abdominal X-ray control was done, showing the right positioning of the internal probe (Figure 6.19, right).

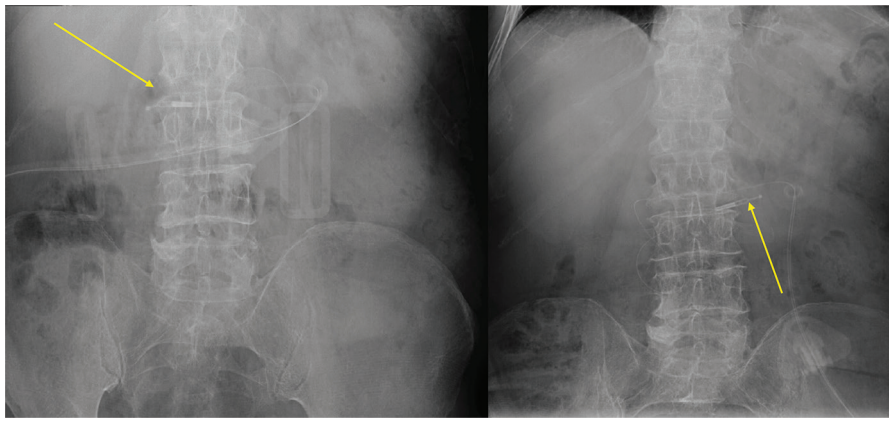

Figure 6.19 LCIG tube mispositioning in stomach (left) and right positioning in ileum (right). Yellow arrow points to the tail of the internal probe.

Table 6.1 Motor's state according to the patient opinion.

Motor fluctuations (according to the patient's opinion)		
	2 weeks after LCIG tube adjustment establishment	**LCIG tube mispositioning**
Morning delayed-on	30 minutes	180 minutes (suboptimal)
"No-on"	Absent	Daily
Wearing-off	20% waking time	50% waking time
Extra dose	Usually not	4-5 times daily
ON–OFF phenomena	Absent	Occasionally

A new measurement period was scheduled with STAT-ON™ in order to objectively verify the worsening state described by the patient. In total, two STAT-ON™ reports were obtained (see the summary in Table 6.2):

- A report 2 weeks after LCIG tube establishment (improvement reported by the patient)
- Four weeks after LCIG tube establishment: patient-reported clinical worsening (LCIG tube mispositioning was detected).

The patient switched from one freezing of gait episode to 4.6 episode per day and walked 124 minutes less each day (26% less than before). The patient also walked 1392 less steps per day on average. A total of 58.4% of inactivity time was reported after probe mispositioning, against 43.2% prior to that change. With the tube right positioned, both OFF and ON times slightly increased due to the patient's activity.

Table 6.2 Summary of the STAT-ON™ report before and after the LCIG tube mispositioning.

	LCIG tube right positioning	LCIG tube mispositioning
FoG episodes	5	41
Fog average per day	1	4.6
Minutes walked per day	59	46.6
Average number of steps	6547.9	5155.3
Total time inactive	43.2	58.4
% Time in OFF	14.8	11.2
% Time intermediate state	18.8	10.9
% Time in ON	23.3	19.5
% Time with dyskinesia	10.8	10.9
Days monitored	13	7
Hours monitored	164.5	88

Discussion: LGIC is a second-line therapy that benefits selected PD patients' quality of life [17, 18]. However, therapy management and supervision are complex, and evaluating the therapy results frequently relies on the patient's opinion.

In the considered case, the etiology for the patient's worsening was a spontaneous wrong placement of the duodenal tube.

STAT-ON™ was useful to objectively quantify the clinical motor situation of PD patient. In this case, the neurologist was able to test motor worsening related to LCIG tube mispositioning compared with the previous clinical situation.

Conclusions and take-home messages:

- STAT-ON™ has been useful to show and quantify the patient's motor improvement or worsening due to the LCIG therapy.
- The monitoring was done in a home environment, and the information obtained was more precise than the clinical features detailed by the patient and his relatives.
- This enormous amount of information could be able to establish certain clinical patterns that point to one cause or another of LGIC dysfunction, in our case, bad placement of the internal probe.

6.11 Monitoring FoG and Second-line Treatment

Responsible professional: Dr. Iria Cabo López
CHUP – Complexo Hospitalario Universitario de Pontevedra. Pontevedra.

Personal history: A 69 year-old Spanish male patient, with a history of ischemic heart disease and dyslipidemia. He was an ex-smoker and had a moderate enolic habit. He was currently taking bisoprolol 5 mg OD, simvastatin 20 mg OD, ranitidine 300 mg OD, tamsulosin 0.4 mg OD, clopidogrel 75 mg OD, and olmesartan 20 mg OD.

Parkinson's disease history: The onset of his Parkinsonian symptoms started in March 2014 with "internal" tremor, slower right movements, and difficulty for walking since about 2 years. A clinical neurological examination revealed mild facial hypomimia, right arm, and leg rigidity ¼, right bradykinesia ¾, and left bradykinesia 2/4. Rest tremor was not present. However, his gait was slow with short steps. His feet stuck to the floor, and his right arm swinging decreased. At the time of diagnosis, UPDRS-II was 1, UPDRS-III was 11, UPDRS-IV was 0, and H and Y = 2.

In summary, the patient presented an akinetic-rigid syndrome with right dominant motor symptoms suggestive of idiopathic Parkinson´s disease. Laboratory test and cerebral magnetic resonance imaging were normal, and treatment with rasagiline and ropinirole was started.

In September 2014, he recognized a deterioration in his Parkinsonian symptoms with a worsening in his motor symptoms, and the dose of ropinirole was increased. In January 2015, levodopa/carbidopa immediate release was started because of motor impairment. There was an important improvement of rigidity and bradykinesia, though freezing of gait (FoG) episodes remained, especially when turning or in narrow places. He remained unchanged until March 2017 when he started with peak-dose dyskinesia and mild wearing-off. He also developed an impulse control disorder (hypersexuality) and a gradual withdrawal of ropinirole was required. In May 2018, axial symptoms became more evident with FoG episodes in his OFF's periods as well as levodopa-induced ON FoG.

Physical examination: In 2019, when the patient was evaluated with the STAT-ON™ for the first time, before initiating treatment with apomorphine, he was taking safinamide 100 mg OD, opicapone 50 mg OD and immediate release carbidopa/levodopa 100 mg five times per day.

Clinical neurological examination revealed left and right arm and leg rigidity ¼, right bradykinesia ¾ and left bradykinesia 2/4, no rest tremor, very slow walking with very reduced step length, his feet stuck to the floor, defragmentation of turns and decreased right arm swing, with several FoG episodes during the physical exam.

OFF: UPDRS-II: 3. UPDRS-III: 34. H and Y 2.5.

- ON: UPDRS-II: 1. UPDRS-III: 16. H and Y 2.
- UPDRS-IV: 3. NMSS: 50. PDSS: 132. FoG-Q: 13.
- Schwab and England: 80%. PDQ-39: 20. WHOQOL-8: 32.

STAT-ON™ objective of use: In December 2019, this patient was evaluated with the STAT-ON™ with the purpose of quantifying OFF/ON time and for the assessment of OFF/ON FoG episodes.

In October 2020, treatment with continuous infusion of apomorphine was initiated, and initial dose was adjusted according to the clinical response until motor control was achieved (infusion rate of apomorphine: 1.05 mL/h).

In December 2021, the patient was evaluated with the STAT-ON™ again, with the purpose of monitoring apomorphine response and assessing changes in FoG episodes.

Diagnosis and decision-making: When the patient was evaluated with STAT-ON™ for the second time in 2021, after initiating apomorphine, his clinical neurological examination revealed right rigidity ¼, left rigidity 0/4, right bradykinesia ¼, left bradykinesia 0/4. His gait improved with better step length and less defragmentation of turns.

- OFF: UPDRS-II: 7. UPDRS-III: 37. H and Y 2.5.
- ON: UPDRS-II: 3. UPDRS-III: 20. H and Y 2.
- UPDRS-IV: 5. NMSS: 30. PDSS: 136. FoG-Q: 10.
- Schwab and England: 90%. PDQ-39: 13. WHOQOL-8: 32.

The first STAT-ON™ report supported the diagnosis of advanced Parkinson´s disease with OFF and ON FoG episodes. The report showed a substantial number of FoG episodes (482) during the 4 days of registration, with an average of 96 episodes of daily FoG. FoG episodes were present in both ON and OFF periods.

Furthermore, average of daily OFF time was 24% while ON time was 21%. The average of OFF hours per day was between 3 and 5.5 h. Therefore, the STAT-ON™ provided confirmation of advanced PD report with more than 3 OFF hours a day, as well as a big number of FoG episodes, which led to instauration of a second-line treatment (Apomorphine infusion therapy).

The second STAT-ON™ report, in 2021, supported an improvement in his motor symptoms and more specifically, in OFF/ON number of FoG episodes. The report showed a substantial reduction in the number of FoG episodes (30) during the 4 days of registration, with an average of 6 episodes

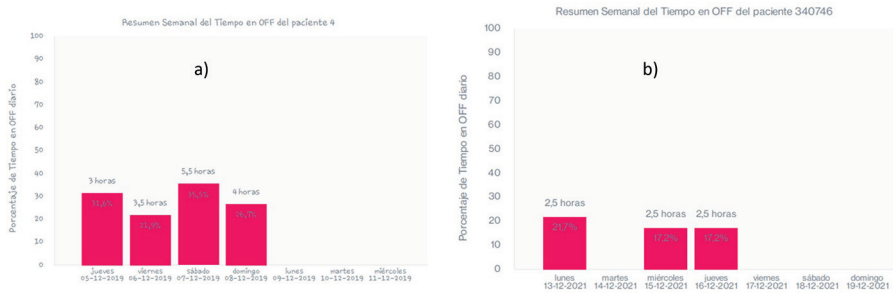

Figure 6.20 Percentage of daily OFF time (A) preapomorphine and (B) postapomorphine.

of daily FoG. Furthermore, average daily OFF time was 13%, while ON time was 46%. The average of daily OFF time was between 0 and 2.5 h a day.

Therefore, the STAT-ON™ reported a global improvement, specifically in OFF and ON time, as well as a reduction of FoG episodes after the instauration of Apomorphine infusion treatment.

Figures 6.20–6.22 show the difference observed between the pre and postapomorphine situations.

Discussion: Certainly, in this case, the device has been very useful to assess the motor fluctuations and the ON FoG episodes, but also to assess the motor state after the onset of a second-line therapy (use of apomorphine).

Conclusions and take-home messages: STAT-ON™ is very useful for completing information provided by the patient or the Hauser diary, providing accurate information about the motor state (ON, OFF, and FoG episodes). It is very useful for monitoring the effects of a second-line treatment.

6.12 Improving Motor Fluctuations with Variable Flow of Apomorphine Subcutaneous Infusion: The Role of STAT-ON™

Responsible professional: Dr. Jorge Hernandez-Vara
Neurology Department and Neurodegenerative Diseases Research group of the Vall d'Hebron University Campus. Barcelona.

Parkinson's disease history: A 73-year-old man was diagnosed with Parkinson´s disease at 58. When he was 69, he experienced motor complications (motor fluctuations and dyskinesias) and was initially managed with oral antiparkinsonian drugs.

At the age of 71, motor fluctuations became refractory to conventional oral medication. At this moment, he was treated with levodopa/carbidopa

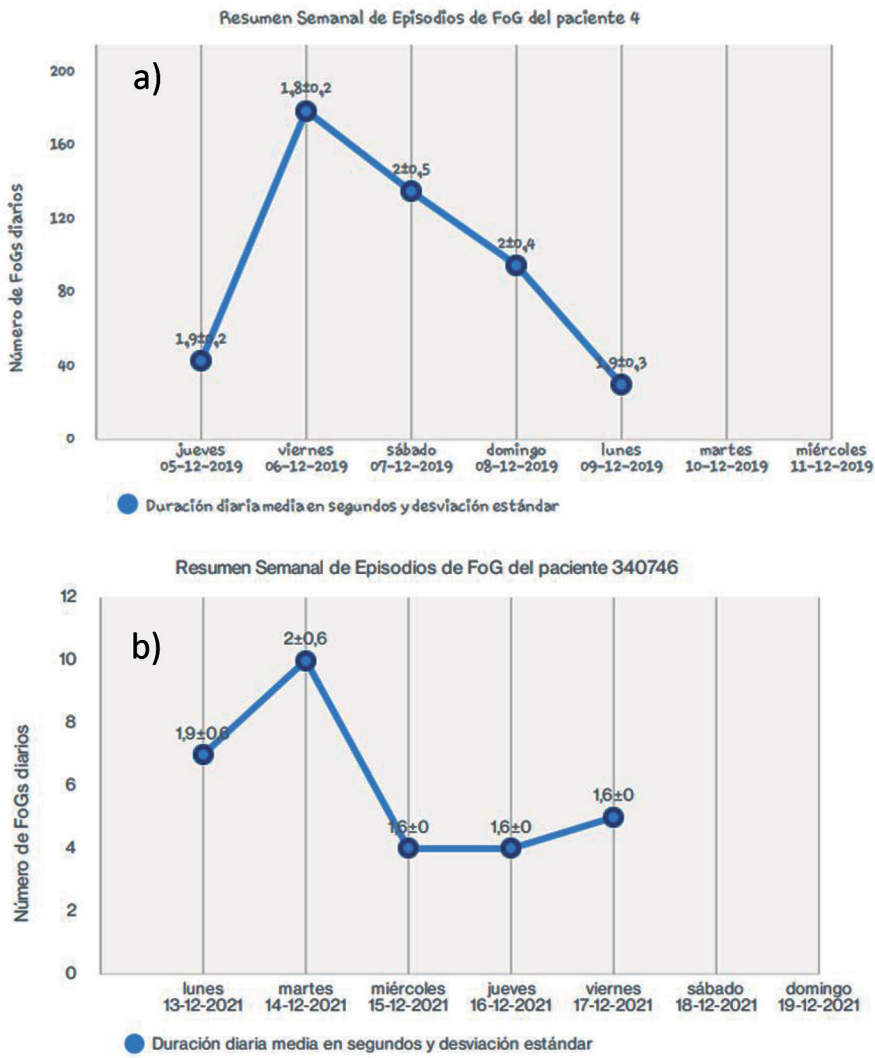

Figure 6.21 Number of FoG episodes per day (dot indicates the average duration) (A) preapomorphine and (B) postapomorphine.

immediate release (100/24 mg) six times per day, levodopa/carbidopa extended release (200/50 mg) once daily, safinamide (100 mg per day) and pramipexole extended release (2.1 mg once daily).

STAT-ON™ objective of use: In order to have an objective reporting of his state and affecting motor fluctuations, the use of the STAT-ON™ device was

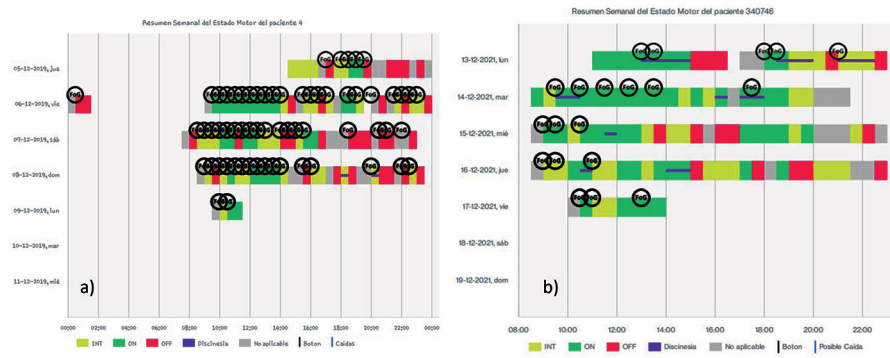

Figure 6.22 STAT-ON™ summary report (A) preapomorphine and (B) postapomorphine.

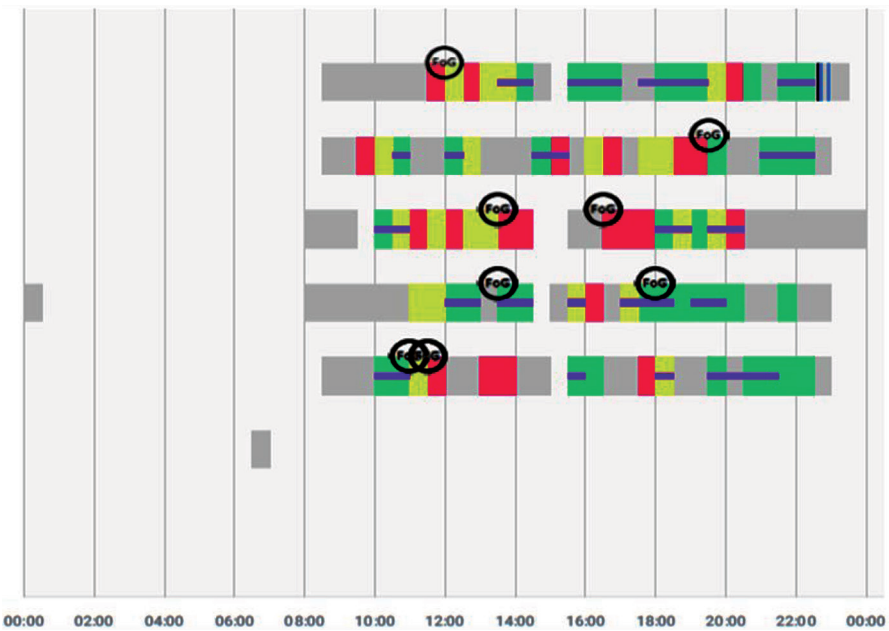

Figure 6.23 STAT-ON™ report summarizes the motor status before starting apomorphine infusion.

decided. Figure 6.23 summarizes the complexity of motor status through the obtained report.

Diagnosis and decision-making: Due to the number of OFF periods and the complexity of motor fluctuations, it was decided to start treatment with subcutaneous apomorphine infusion during the waking day (16 h). The number of hours of inactivity in the report is remarkable, especially in the morning.

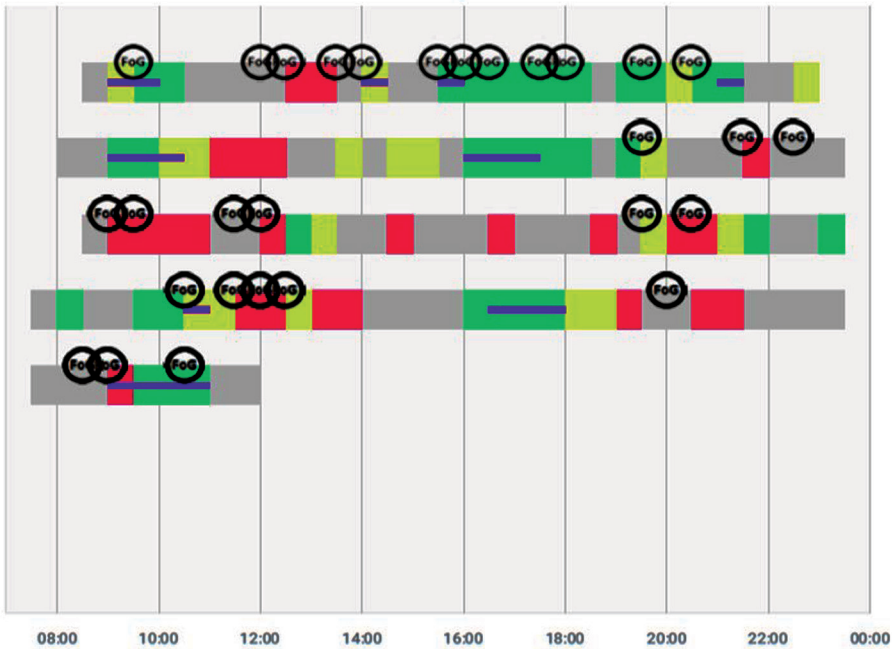

Figure 6.24 Motor status in terms of motor complications after 3 months of subcutaneous apomorphine infusion (with the constant flow).

Figure 6.24 summarizes the motor status in terms of motor complications after 3 months of subcutaneous apomorphine infusion treatment with a flow of 1 mL/h for 16 h. The patient was treated with levodopa/carbidopa immediate release (100/25 mg) six times per day and levodopa/carbidopa extended release (200/50 mg) at bedtime.

Despite apomorphine infusion, motor fluctuations persisted, and nocturnal akinesia was more evident and disabling for the patient. For these reasons, we decided to set the pump with three different flows to improve the motor status of the patient. From 7 am to 12 am the flow was set at 1.2 mL/h, from 12 pm to 11 pm at 1.0 mL/h and from 11 pm to 7 am at 0.4 mL/h.

Figure 6.25 presents the motor status after 6 months of apomorphine infusion and 3 months of variable flows. The patient reported a good response during the night with better overall sleep quality. The motor status improved clearly compared with the baseline in terms of mobility and OFF periods.

Conclusions and take-home messages: In summary, STAT-ON™ is a very useful tool to monitor mobility in advanced Parkinson´s disease patients and can be used as a guide for therapeutic decision-making, including variable flow adjustment of the infusion strategy.

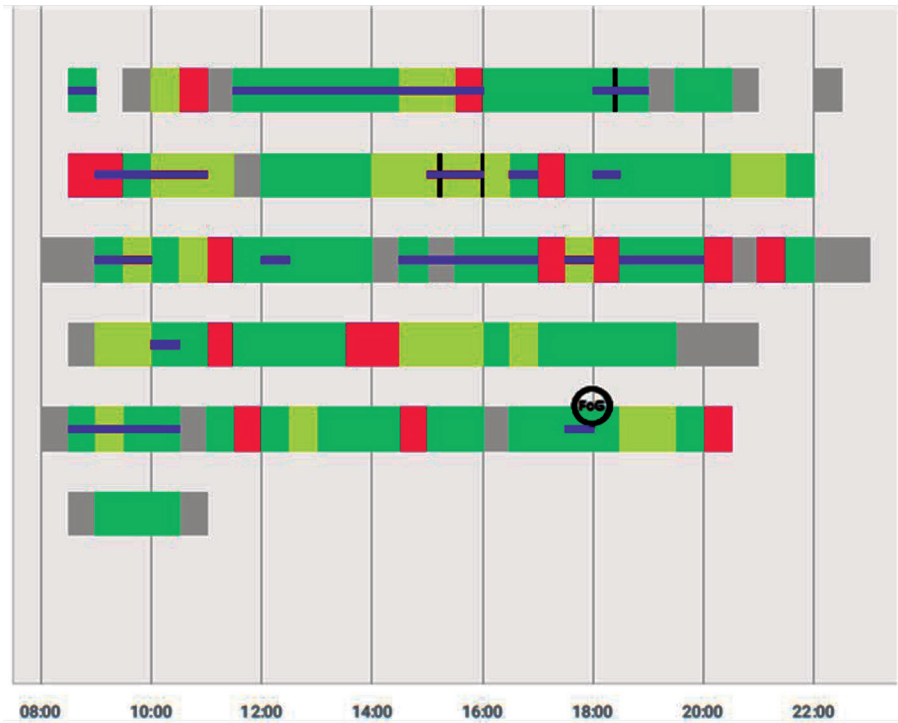

Figure 6.25 Improvement of motor fluctuations, especially in the morning, after 3 months of subcutaneous apomorphine infusion with variable flow.

6.13 Simultaneous Recording of Motor Activity with the STAT-ON™ Device and Subthalamic Nucleus Field Potentials (Percept™) in Parkinson's Disease

Responsible professionals: Dr. José Maria Barrios López and Dr. Lucía Triguero
Hospital Universitario Virgen de las Nieves. Granada.

Personal history: Maternal family history of myasthenia gravis and diabetes mellitus in some relatives and personal history of tonsillectomy.

Parkinson's disease history: A 40-year-old man with advanced juvenile Parkinson's disease (PD) secondary to a homozygous mutation of the PARK2 gene, with a disease course of 34 years. At the age of 6 years, he progressively developed gait impairment due to episodes of dystonia in the left foot. Later, in adolescence, he started with a left-hand tremor. Clinical symptoms improved and remained stable for a few years after starting treatment with levodopa/benserazide and pramipexole.

During the follow-up, a comprehensive workup was performed, including laboratory tests, a normal brain magnetic resonance imaging, and a DaTSCAN which revealed significantly decreased presynaptic dopaminergic transporters in both striatal nuclei. Additionally, a genetic study of dystonia was negative, and finally, a homozygous pathogenic variant of the PARK2 gene was discovered.

During the course of the disease, he began to develop motor complications with simple and complex fluctuations (including delayed ON, wearing-off, and severe OFF state with tremor and asymmetric stiffness predominantly in the left arm and lower limbs, back and leg pain, and inability to walk), peak-dose and possible biphasic dyskinesias.

He was also diagnosed with a psychotic episode related to dopamine agonists. Different treatments were tested, including levodopa/benserazide, pramipexole, ropinirole, rasagiline, and opicapone. Considering the motor complications, treatment was adjusted with levodopa/benserazide (200/50 mg) six times a day, ropinirole retard (2 mg) every other day, and opicapone (50 mg) daily.

Physical examination: Examination in ON state (UPDRS-III 11; Hoenh and Yahr stage II): facial hypomimia ¼, no hypophonia or dysarthria. Mild resting tremor in left arm ¼. No stiffness. Bradykinesia in the left extremities 1-2/4. Choreic/dystonic dyskinesias in the feet. Standing upright is possible without support. Gait with reduced swinging of the left arm. Negative pull test.

Examination in OFF state (UPDRS-III 55; Hoenh and Yahr stage IV): facial hypomimia and hypophonia 2/4. Resting and action tremor predominantly in the left arm and right leg (both ¾). Generalized stiffness, 2/4 axial and ¾ in all four extremities. Global bradykinesia, 2/4 in the right limbs and ¾ in the left limbs. Standing upright is possible without support. Gait with short steps, frequent freezing at start and turn, and choreic/dystonic movements of both feet. Positive pull test (3/4).

Advanced juvenile PD secondary to homozygous mutation of the PARK2 gene with simple and complex motor fluctuations and dyskinesias predominantly in the lower limbs with gait interference was diagnosed. Treatment with bilateral subthalamic nucleus deep brain stimulation (STN-DBS) with the Percept™ neurostimulator (Medtronic) was decided.

STAT-ON™ objective of use: The objective was to describe in clinical practice the simultaneous recording of local field potentials (LFPs) using Percept™ and the motor status using STAT-ON™ in a patient with PD, who underwent bilateral STN-DBS, in order to optimize the treatment.

Once the anatomical location of the electrodes was verified and before starting continuous stimulation, LFPs with Percept™ and motor activity with

STAT-ON™ were recorded for one week. In addition, the patient marked different events: best ON worst OFF; generalized ("dose peak") and leg ("biphasic") dyskinesias; and medication intake. Finally, we analyzed if there was a correlation between the marked events and the recording of both systems.

Diagnosis and decision-making: During the recording period, synchronicity was observed between the events marked by the patient and the results of the STAT-ON™ and Percept™ devices (Figure 6.26). To be emphasized:

- The OFF periods are in agreement with STAT-ON™ OFF state recordings and beta bands.
- Conversely, ON periods are in coincidence with the absence of beta bands, the presence of gamma bands, and non-OFF states reported by STAT-ON™.
- "Dose peak" dyskinesias coincided with dyskinesias identified by STAT-ON™, that is, with gamma bands and without beta bands.
- On the other hand, "biphasic" dyskinesias coincided with a beta band.
- The STAT-ON™ device also detected episodes of FoG, most of them coinciding with "OFF" states and beta bands.

After initiation of bilateral STN-DBS, a decrease in the daily recording of beta bands was observed, coinciding with the disappearance of tremor and stiffness, and substantial improvement in global bradykinesia and gait. On subsequent visits, the stimulation parameters were adjusted, allowing the levodopa/benserazida dose to be reduced and ropinirole to be discontinued, thereby decreasing motor fluctuations and dyskinesias.

Discussion: In our patient undergoing bilateral STN-DBS with the Percept™ system, concordance was observed in the simultaneous recording of motor complications with LFPs and STAT-ON™. In addition, STAT-ON™ was also able to detect FoG and different degrees of motor status. Therefore, this device could be useful in the outpatient monitoring of motor complications in patients with PD treated with DBS in order to optimize therapeutic management.

Conclusions and take-home messages: Outpatient monitoring of motor complications with new technologies is a complementary tool to the anamnesis and clinical evaluation of patients with PD, allowing a more precise assessment of the patient's daily motor status. For example, the recording of LFPs allows more physiological and accurate monitoring, while the

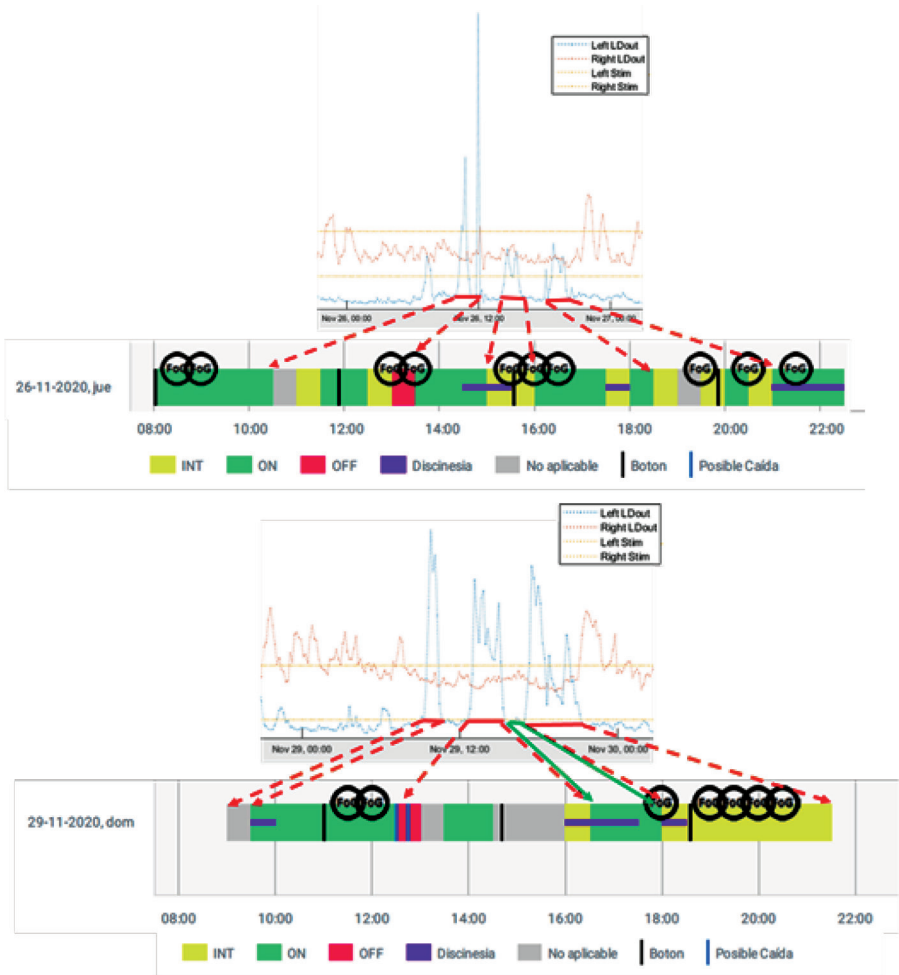

Figure 6.26 Correlation between daily recordings of beta bands and motor status according to Percept™ and STAT-ON™, respectively. Beta bands (blue spikes in the top graph) coincide with OFF (red), "intermediate" (yellow) or "not applicable" (gray = no motion detected) motor status periods detected by STAT-ON™. The ON periods (green) coincide with beta-band free intervals. Most freezing of gait (FoG) episodes detected by STAT-ON™ coincide with non-ON periods.

STAT-ON™ device provides a noninvasive recording and enables the detection of FoG episodes [19, 20].

In our patient with PD who underwent STN-DBS, we confirmed concordance in the indirect recording of motor complications with STAT-ON™. Therefore, the device can be a useful tool in therapeutic optimization in patients who underwent DBS.

6.14 Telemedicine in Parkinson's Disease: The Role of STAT-ON™

Responsible professionals: Dr. Alvaro García-Bustillo and Dr. Esther Cubo
Movement Disorders Unit. Hospital Universitario de Burgos. Burgos.

Personal history: Female, 75-year-old, right-handed, her medical history is significant for arterial hypertension and hypercholesterolemia. From family history, her father had Parkinsonism and dementia at the age of 70 years.

Parkinson's disease history: She consulted at the age of 72 due to a history of rest tremor and kinetic tremor, predominant in the right extremities for one year. She did not have cognitive impairment, predominant dysautonomic symptoms, or early gait impairment. Based on the neurological exam, significant for normal cognitive status, mild bradykinesia, and rigidity, and decreased right arm swing with normal postural responses, she was diagnosed with PD according to the MDS-criteria [21], with a Hoehn and Yahr stage of 2.

She was stable for few years with a good response to levodopa (300 mg/day). In follow-up, 5 years later, her motor status started deteriorating with falls, motor fluctuations, and mild dyskinesias with incomplete response to treatment adjustments. She could not receive dopaminergic agonists due to the presence of mild hallucinations. Based on her risk of falling and unclear history of timing for her OFF periods, she was included in a telemedicine, multidisciplinary program [22] with occupational therapists, nurses, and neurologists to improve balance and motor fluctuations.

Physical examination: The patient was evaluated at a baseline visit and 4 months later. We completed the following assessments: The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [23], for motor status severity and disability; Freezing of Gait Questionnaire (FoG-Q) [24], and the Mini Balance Evaluation System Test (Mini-BESTest), for balance, postural control, sensory orientation, and dynamic gait assessment; Non-Motor Symptoms Scale (NMSS), for the assessment of the non-motor symptoms; The Parkinson's Disease Questionnaire (PDQ-39), for health-related quality of life. The results of these assessments are shown in Table 6.3.

STAT-ON objective of use: This patient was diagnosed with PD with motor fluctuations, gait impairment, and falls. Given the high risk for hallucinations with an increased dose of dopaminergic drugs, it was decided to include

Table 6.3 Results of the assessments pre and postmultidisciplinary telemedicine program.

	Basal visit	4 months visit	Improvement percentage
MDS-UPDRS (total score)	56	43	23.21
MDS-UPDRS (part III score)	42	31	26.19
FoG-Q	5	4	20.00
Mini-BESTest	21	24	14.29
NMSS	19	15	21.05
PDQ-39	15	13	13.33

* In the MDS-UPDRS, FOG-Q, NMSS and PDQ-39 lower score indicate better status, while in Mini-BESTest lower scores indicate worse status. Improvement percentage was calculated as (final score-baseline score)/baseline score.

her in a multidisciplinary telemedicine program. In this program, the patient received monthly teleconsultations with neurologists and nurses and weekly telerehabilitation sessions with occupational therapists for 4 months.

The objectives were to improve her quality of life by decreasing the risk of falling, increasing physical activity, and improving balance and gait by adjusting her PD medications based on the presence of off periods and disabling dyskinesias.

Additionally, it was decided to monitor her Parkinsonian motor symptoms with STAT-ON™ with the following objectives:

- Adjusting the antiparkinsonian medications based on the timing and duration of the OFF periods.
- Monitoring the frequency of falls and their relationship with the OFF periods.
- Assessing the amount of physical activity as a therapeutic target for physical therapy intervention.
- Evaluating the usability of wearable sensors in patients with advanced PD.

Diagnosis and decision-making: To achieve these goals, she wore the STAT-ON™ device, while she was performing her daily living activities. Baseline and 4-months (after completing the multidisciplinary telemedicine program) assessments provided by STAT-ON™ are shown in Table 6.4.

Discussion: In addition to the PD clinical information provided by the PD rating scales, assessing motor and gait/balance severity, nonmotor symptoms, and quality of life, STAT-ON™ was able to provide additional motor information while the patient was performing her daily living activities.

Table 6.4 Summary of the motor status measured by STAT-ON™ at the baseline visit and after 4 months of the program.

	Baseline visit	4-months visit
Monitored days	8	7
Monitored time (hours)	99.5	85
Number FoG episodes	2	0
Av. FoG episodes/day	0.2 ± 0.4	0 ± 0
Average walking minutes/day	99.7 ± 29.6	108.9 ± 14
Average number steps/day	9959.5 ± 3026.9	10,892 ± 1765.5
Total time in OFF state	39.5 h (39.7%)	28 h (32.9%)
Total time in intermediate state	27 h (27.1%)	19.5 h (22.9%)
Total time in ON state	22.5 h (22.6%)	28.5 h (33.6%)
Total time with dyskinesia	12 h (12.1%)	7 h (8.2%)

With STAT-ON™, we were able to visualize the worst OFF periods, FoG episodes, and the presence of falls and ON periods with dyskinesias. Based on STAT-ON™ reports, we advised her to increase physical activity, and slightly increased the levodopa dose with higher doses in the evening without significantly increasing the hallucinations.

Of note, this patient was satisfied with STAT-ON™ after using it for a relatively long time. The adherence to new technologies and the easiness of using them for patients with advanced age are still controversial. In this case, our patient was living with her husband, who was cognitively intact and eager to use new technologies. We obtained remote information for 4 months, facilitating the PD adjustments based on her motor fluctuations and nonpharmacological interventions, promoting physical activity. However, there is no doubt that the support of her husband and the education provided by the health professionals contributed to overcoming the barriers to using wearables in these populations.

With the clinical information provided by the combination of STAT-ON™ plus standard PD rating scales, we could monitor the treatment response, progression of her disease, and the success of our novel, multidisciplinary telemedicine intervention. In addition, the evaluation of STAT-ON™ reports by the neurologist was not considered high-time consuming.

Conclusions and take-home messages: PD may be considered particularly fitting for distance health/remote assessments with wearable sensors because of the critical importance of the presence, distribution, and characteristics of OFF periods, dyskinesias, and gait impairment. PD patients, especially those with advanced age and living in remote areas, have increased difficulty accessing movement disorder neurologists and other health professionals.

The combination of standard clinical information obtained in in-office consultations, plus remote assessments provided by STAT-ON™, allows better therapeutic management of PD motor symptoms.

6.15 Conclusion

The validation of a medical device by health professionals, during the normal exercise of their activity, is one of the necessary steps to be covered in the acceptation way of a new product introduced into the market. Since 2019, when STAT-ON™ obtained its CE marking as class IIa medical device, the promotion and diffusion activity among the neurologists, hospitals, movement disorders units, and health professionals has been a prominent activity done by the manufacturer.

This chapter has presented a collection of 13 real use cases developed in different Spanish hospitals, using STAT-ON™ as a complementary technology tool that has been used with a diversity of objectives, arriving to determine the usefulness of the device for several reasons (helping the doctor to improve the therapy, identifying candidates to SLT, contributing to a better adjustment of infusion variable dosage, improve the awareness of the patient, complementing or substituting the patient's diary, etc.). The summary of the use cases with the main conclusions is provided in Table 6.5.

References

[1] Kleiner G, Fernandez HH, Chou KL, Fasano A, Duque KR, Hengartner D, et al. 'Non-Motor Fluctuations in Parkinson's Disease: Validation of the Non-Motor Fluctuation Assessment Questionnaire'. Mov Disord. 2021;36(6):1392–1400.

[2] Martínez-Fernández R, Schmitt E, Martinez-Martin P, Krack P. 'The hidden sister of motor fluctuations in Parkinson's disease: A review on nonmotor fluctuations. Mov Disord 2016;31(8):1080–94.

[3] Kim A, Kim HJ, Shin CW, Kim A, Kim Y, Jang M, et al. 'Emergence of non-motor fluctuations with reference to motor fluctuations in Parkinson's disease'. Parkinsonism Relat Disord 2018;54:79–83.

[4] Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, et al. 'Nonmotor fluctuations in Parkinson's disease: frequent and disabling'. Neurology 2002;59(3):408–13.

[5] Antonini A, Martinez-MartinP, Chaudhuri RK, Marello M, Hauser R, Katzenschlager R, et al. . 'Wearing-Off Scales in Parkinson's Disease:

Table 6.5 Summary of the presented real use cases.

Case	Title	Age	Sex	Center/hospital	Location	Main conclusions and benefits.
2	Early detection of motor fluctuations	65	Male	Centro Médico TEKNON	Barcelona	• Verification of motor fluctuations • Treatment adjustment • Awareness of patient
3	Improving awareness of the first motor fluctuations	59	Male	Complex Hospitalari Moisès Broggi	Sant Joan d'Espí	• Detection of early fluctuations. • Patient's awareness.
4	Complimenting a poor patient's interview about her motor complications	61	Female	Hospital Parc Taulí	Sabadell	• Substitution of patient's diaries. • Detection of OFF states.
5	Indirect detection of probable PD nonmotor fluctuations	67	Female	Complex Hospitalari Moisès Broggi	Sant Joan dÈspí	• Help neurologist to identify NMF in association with MF.
6	Deciphering the patient's complaints using STAT-ON™	68	Female	Centro Médico TEKNON	Barcelona	• Precise identification of OFF states and dyskinesia • Patient's education of the knowledge about motor symptoms.
7	Ambulatory monitorization of a patient with advanced PD	70	Female	Hospital Universitario de Toledo	Toledo	• Education of the patient in the relationship between MF and medication intakes. • Decision for an SLT.
8	Improvement of the patient's awareness of the advanced PD stage and the need of second-line treatment	73	Female	Hospital Verge de la Cinta	Tortosa	• Detection of a candidate for an SLT • Objective identification of ON–OFF periods.

9	Identification of candidates to device-aided therapy	58	Female	Complejo Hospitalario Universitario de A Coruña	A Coruña	• Identification of FoG presence • Better adjustment of Duodopa therapy.
10	STAT-ON™ use for LCIG tube adjustment	73	Male	Hospital Universitario Infanta Leonor	Madrid	• Quantification of improvement/ worsening of the patient due to LCIG therapy.
11	Monitoring FoG and second-line treatment	69	Male	Complexo Hospitalario Universitario de Pontevedra	Pontevedra	• Complementary information to the Hauser diary • Monitoring a SLT results.
12	Improving motor fluctuations with variable flow of apomorphine subcutaneous infusion. The role of STAT-ON™	73	Male	Campus Universitario Vall d'Hebron	Barcelona	• Therapeutic decision-making • Contribution to the variable flow adjustment of a subcutaneous infusion strategy.
13	Simultaneous recording of motor activity with the STAT-ON™ device and subthalamic nucleus field potentials (PERCEPT™) in PD	40	Male	Hospital Universitario de Burgos	Burgos	• Confirmation of the relationship between MF (recorded with STAT-ON™) and the LPF (recorded with Percept™) in a DBS-implanted patient.
14	Telemedicine in PD. The role of STAT-ON™	75	Female	Hospital Universitario de Burgos	Burgos	• Contribution to the improvement of the therapeutic management of advanced age PD patients, living in rural areas.

Critique and Recommendations'. Mov Disord 2011 Oct;26(12):2169–75. doi: 10.1002/mds.23875. Epub 2011 Jul 20.

[6] Goetz CG, Stebbins GT, Chmura TA, Fahn S, Poewe W and Tanner C. 'Teaching program for the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale: (MDS-UPDRS)'. Movement Disorders 2010; Jul 15;25(9):1190–4. doi: 10.1002/mds.23096.

[7] Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CFO, et al. 'A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia'. Clin Neuropharmacol 2000; 23(2):75–81. doi: 10.1097/00002826-200003000-00003.

[8] Espay A, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. 'Technology in Parkinson's disease: challenges and opportunities'. Mov Disord 2016 Sep;31(9):1272–82. doi: 10.1002/mds.26642. Epub 2016 Apr 29.

[9] Pérez-López C, Samà A, Rodríguez-Martín D, Moreno-Aróstegui JM, Cabestany J, Bayés À, et al. 'Dopaminergic-induced dyskinesia assessment based on a single belt-worn accerelometer'. Artif Intell Med 2016 Feb;67:47–56. doi: 10.1016/j.artmed.2016.01.001. Epub 2016 Jan 14.

[10] Rastgardani T, Armstrong MJ, Gagliardi AR, Marras C. 'Understanding, Impact, and Communication of "Off" Periods in Parkinson's Disease: A Scoping Review'. Mov Disord Clin Pract. 2018 Oct 9;5(5):461–470. doi: 10.1002/mdc3.12672. PMID: 30515435; PMCID: PMC6207105.

[11] Montanaro E, Artusi CA, Zibetti M, Lopiano L. 'Complex therapies for advanced Parkinson's disease: what is the role of doctor-patient communication?' Neurol Sci. 2019 Nov;40(11):2357–2364. doi: 10.1007/s10072-019-03982-5. Epub 2019 Jun 28. PMID: 31254180.

[12] Antonini A, Stoessl AJ, Kleinman LS, et al. 'Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach'. Curr Med Res Opin 2018;34:2063–73.

[13] Martinez-Martin P, Kulisevsky J, Mir P, Tolosa E, García-Delgado P, Luquin MR. 'Validation of a simple screening tool for early diagnosis of advanced Parkinson's disease in daily practice: the CDEPA questionnaire'. NPJ Parkinsons Dis. 2018 Jul 2;4:20.

[14] Santos García D, López Ariztegui N, Cubo E, et al. 'Clinical utility of a personalized and long-term monitoring device for Parkinson's disease in a real clinical practice setting: An expert opinion survey on STAT-ON™'. Neurologia (Engl Ed) 2020:S0213–4853(20)30339-X.

[15] Bougea A, Palkopoulou M, Pantinaki S, Antonoglou A, Efthymiopoulou F. 'Validation of a real- time monitoring system to detect motor symptoms in patients with Parkinson's disease treated with Levodopa Carbidopa Intestinal Gel [abstract]'. Mov Disord (2021). Available online at: https://www.mdsabstracts.org/abstract/validation-of-a-real-time-monitoring-system-to-detect-motor-symptoms-in-patients-with-parkinsons-disease-treated-with-levodopa-carbidopa-intestinal-gel/ (accessed May 12, 2022).

[16] Barrios-López JM, Ruiz Fernandez E, Triguero Cueva L, et al. 'Registro simultáneo de la actividad motora con sensores inerciales (STAT-ON™) y de potenciales de campo de núcleo subtalámico (PerceptTM) en la enfermedad de Parkinson'. XLIII Reunión Anual Sociedad Andaluza Neurología Sevilla (2021).

[17] Olanow CW, Kieburtz K, Odin P, Espay AJ, et al. 'Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study'. Lancet Neurol. 2014 Feb;13(2):141–9. doi: 10.1016/S1474-4422(13)70293-X.

[18] Hubert H Fernandez, James T Boyd, Victor S C Fung, et al. Long-term safety and efficacy of levodopa-carbidopa intestinal gel in advanced Parkinson's disease. Mov Disord. 2018 Jul;33(6):928–936. doi: 10.1002/mds.27338.

[19] Neumann W-J, Staub F, Horn A, Schanda J, Mueller J, Schneider G-H, et al. 'Deep brain recordings using an implanted pulse generator in Parkinson's disease'. Neuromodulation. 2016;19(1):20.

[20] Neumann W-J, Staub-Bartelt F, Horn A, Schanda J, Schneider G-H, Brown P, et al. 'Long term correlation of subthalamic beta band activity with motor impairment in patients with Parkinson's disease'. Clin Neurophysiol. 2017;128(11):2286.

[21] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. 'MDS clinical diagnostic criteria for Parkinson's disease'. Mov Disord [Internet]. 2015 [cited 2022 Oct 28]; 30(12): 1591–1601. Available from: https://doi.org/10.1002/mds.26424

[22] Cubo E, Garcia-Bustillo A, Arnaiz-Gonzalez A, Ramirez-Sanz JM, Garrido-Labrador JL, Valiñas F, et al. 'Adopting a multidisciplinary telemedicine intervention for fall prevention in Parkinson's disease. Protocol for a longitudinal, randomized clinical trial'. PLoS One [Internet]. 2021 [cited 2022 Oct 28]; 16(12). Available from: https://doi.org/10.1371/journal.pone.0260889

[23] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. 'Movement Disorder Society-sponsored revision of the

Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results: MDS-UPDRS: Clinimetric Assessment'. Mov Disord [Internet]. 2008 [cited 2022 Oct 28]; 23(15): 2129–2170. Available from: https://doi.org/10.1002/mds.22340

[24] Giladi N, Tal J, Azulay T, Rascol O, Brooks DJ, Melamed E, et al. 'Validation of the freezing of gait questionnaire in patients with Parkinson's disease: Validation of FOG Questionnaire'. Mov Disord [Internet]. 2009 [cited 2022 Oct 28]; 24(5): 655–661. Available from: https://doi.org/10.1002/mds.21745