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Clara Fleischman

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Clara Fleischman. Towards the integration of body-worn sensors in the management of Parkinson's disease: perspectives on new paradigms of follow-up. Human health and pathology. Sorbonne Université, 2021. English. NNT : 2021SORUS118 . tel-03467730

HAL Id: tel-03467730

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Sorbonne Université

Ecole Doctorale Cerveau Cognition Comportement (ED n°158)

Paris Brain Institute

Centre EXPLOR ! Air Liquide Healthcare

Towards the integration of body-worn sensors in the
management of Parkinson's disease: perspectives on
new paradigms of follow-up

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Thèse de doctorat de Neurosciences

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Présentée et soutenue publiquement le Mardi 16 Février 2021

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Remerciements

Bien plus que de développer mes connaissances et mes compétences en recherche, le doctorat m'a apporté la richesse des interactions avec les personnes que j'ai eu la chance de rencontrer pendant ces quatre dernières années. Je tiens à les remercier car elles ont participé à ce qu'a pu devenir ce travail.

Tout d'abord, je remercie particulièrement mon directeur de thèse et mon responsable scientifique, Pr David Grabli et Dr Yann Rétory. Le premier pour son expertise, sa vision positive qui a largement participé à la gestion des rebondissements, et sa confiance pour se lancer dans l'aventure de cette thèse. Le second pour ses conseils pertinents et son coaching qui m'a aidée à gravir les - petites - montagnes du doctorat... Je suis très reconnaissante de leur implication et leur énergie mises dans ce projet pour m'aider à réaliser les objectifs. J'ai énormément appris de nos sessions de travail et nos échanges.

Je remercie Pr Dominique Guehl et Pr Djamel Bensmail d'avoir accepté d'être rapporteurs de cette thèse. Je remercie aussi Pr Marie Vidailhet, Dr Ana Marques, Pr Marie-Laure Welter et Pr Pascale Pradat-Diehl d'avoir accepté de consacrer du temps pour apporter un regard critique sur ce travail et le juger.

Je tiens à remercier Dr Michel Petitjean, Pr David Devos et Pr Bertrand Degos pour leurs avis instructifs et précieux conseils lors des comités de suivi.

Je tiens à adresser toute ma reconnaissance à Sébastien Hardy, auprès de qui j'ai beaucoup appris pour gérer les revirements de situations et qui m'a accordé sa confiance pour mettre en place ce projet. J'ai le sentiment d'avoir progressé professionnellement et personnellement aussi grâce à son accompagnement et ses mots justes.

J'adresse de sincères remerciements à mon équipe du Centre EXPLOR! qui m'a permis d'évoluer dans un environnement dynamique et convivial. Ces remerciements sont chaleureusement étendus à la PMT avec laquelle j'ai eu le plaisir de passer des moments aussi sérieux que drôles. Ces amitiés partagées ont été inestimables pendant les petits et grands succès comme dans les périodes compliquées. Sans pouvoir les citer tous, je remercie Eugénie pour son écoute et son énergie, Flavien pour ses idées et ses blagues sans limite et sa formation en Python, Carine pour sa gentillesse et sa bonne humeur constantes, Shuo pour sa délicatesse, Charles-Philippe pour ses punchlines, Kaixian pour sa sincérité et son humour, les achats PND pour leur ténacité à mettre l'expertise en avant, Fanny pour sa présence toujours positive, Laurie pour ses encouragements, Dorra pour son optimisme éclairé... Je remercie Sylvain qui m'a

permis d'avancer soutenue et bien accompagnée dans ces aventures, en plus de m'avoir ouvert la porte d'Explor. Je remercie Pauline et Baptiste d'avoir pris ce chemin avec nous et de m'avoir apporté beaucoup de soutien et d'encouragements sur la fin de ma thèse. Je leur souhaite la plus grande réussite ! J'adresse toute ma gratitude à Pauline pour son aide dans tous les domaines et sa présence rassurante. J'ai une pensée pour les stagiaires et alternants qui ont aussi rendu le quotidien agréable à Explor. Je remercie Alexandra Schmidt pour son intérêt envers mon travail et ses conseils avisés.

Je remercie plus largement la société ALEHOS Development devenue ALHIST qui m'a accueillie pour cette thèse.

J'adresse aussi des remerciements aux collaborateurs d'Air Liquide avec qui j'ai eu des échanges de qualité. Je remercie les collaborateurs des filiales qui m'ont impliquée dans des projets m'amenant à partager mon travail. Mille mercis à Véronique Crône et Olivier Ponton d'avoir rendu cette thèse possible, à Aude Milet pour ses conseils si précieux...

Je remercie l'ICM qui a été un partenaire clé et qui m'a permis de rencontrer des personnes formidables pendant cette thèse et même bien avant. Je remercie Pr Jean-Christophe Corvol qui m'a permis d'intégrer une équipe de recherche très accueillante, merci MPP+.

Je remercie tous les membres du CIC qui forment plus qu'une équipe au sein de l'ICM et avec qui j'ai été très heureuse de passer des bons moments. Je pense à chacun avec qui j'ai pu partager un repas ou même des discussions de couloir.

Cette thèse n'aurait pas eu le même quotidien sans l'auto-proclamé Data Lab et deux co-bureaux aussi généreux en amitié que déterminés dans le travail. Un énorme merci à Samir pour sa sagesse et sa résistance inspirante et communicative. Un immense merci à Marion, avec qui j'ai partagé bien plus que des prises de tête interminables sur les analyses. Je dois énormément à son travail expert et à nos longues discussions.

Je remercie le service de neurologie de la Pitié-Salpêtrière, j'ai côtoyé des experts très avenants et passionnés. Merci à Arlette Welaratne, Lise Mantsi et Hélène Letrillart pour leur disponibilité et leurs connaissances essentielles des patients. Un grand merci à Elise Corsetti pour les heures passées à récupérer des informations cachées partout.

Je pense aux patients courageux, et aux neurologues que j'ai vus dévoués dans leur travail de soin et pour faire progresser la recherche. Je remercie les participants aux études qui ont fait preuve d'un réel engagement dans leurs tâches pour m'aider.

Je remercie aussi l'ANRT qui a financé cette thèse CIFRE. J'ai beaucoup apprécié évoluer entre l'entreprise et le laboratoire, dans des milieux différents mais complémentaires.

Finalement, la thèse a aussi été un équilibre à trouver entre la vie professionnelle et la vie personnelle. Donc je tiens à remercier énormément mes proches qui m'ont soutenue et encouragée tout au long de mes études et de cette thèse.

Mes ambitions de doctorat ont certainement été influencées par Fatma, Isaac, Sophie...dont les travaux à l'ICM ont été inspirants. Merci de m'avoir soutenue en connaissance de cause !

Je remercie les fabuleux The Usual et apparentés pour leur amitié géniale et tous ces moments mémorables qui ont rendu ces dernières années encore plus plaisantes.

Je remercie aussi les amis d'exception que j'ai rencontrés à Paris Descartes et à PSL-ITI, et qui m'ont fait découvrir leurs univers.

Bien sûr, je n'aurais pas pu faire tout ce travail sans l'amour et le soutien indéfectible de ma famille. L'aboutissement de cette thèse a été possible grâce à mes parents du meilleur soutien. Merci énormément de croire en moi, de toujours m'encourager à aller plus loin à chaque étape et de m'avoir donné la force et l'envie de persévérer. Je remercie aussi mon frère, mon neveu et ma nièce pour tous les instants magiques qui m'ont ressourcée en tout temps. Enfin, je remercie Léonard pour son soutien inconditionnel et ses encouragements quotidiens, son réconfort dans les moments de doute ou de difficultés, et sa force pour nous amener vers la réussite avec confiance.

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List of Scientific Contributions

This thesis work has been valued by the writing of articles currently being published in international peer-reviewed journals, and by communication through posters at national and international congresses.

List of publications

- Virbel-Fleischman C, Houot M, Rétory Y, Hardy S, Corsetti E, Saverot A, Berthelot E, F, Bendetowicz D, Villain N, Tarrano C, Mantsi L, Letrillart H, Vidailhet M, Corvol JC, Degos B, Roze E, and Grabli D. 2020. "How Treatment Is Adapted in Parkinson's Patients under Apomorphine: A Two-Year Retrospective Study." *Submitted, 2020.*
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- Virbel-Fleischman C, Rétory Y, Hardy S, Huiban C, Corvol JC, and Grabli D. 2020. "Body-Worn Sensors for Parkinson's Disease: A Qualitative Approach with Patients and Healthcare Professionals." *Submitted, 2020.*
- Virbel-Fleischman C and Grabli D. "Apport de l'actimétrie" in Apports des nouvelles technologies, from Defebvre, L., & Vérin, M. (2020). La maladie de Parkinson. Masson Elsevier

List of communications in congresses

- Virbel-Fleischman C, Hardy S, Corvol JC, and Grabli D. Mesure d'actimétrie dans la maladie de Parkinson, quelle pertinence clinique ? Congrès JNLF April 2018. Revue Neurologique Avril 2018.
- Virbel-Fleischman C, Rétory Y, Liu S, Hardy S, Corvol JC, and Grabli D. Accelerometer-based measures and analyses of nonmotor symptoms of patients with Parkinson's Disease. MDS Congress October 2018.

- Virbel-Fleischman C, Rétory Y, Hardy S, and Grabli D. Acceptabilité et expérience utilisateur de patients et de professionnels de santé à propos de dispositifs d'actimétrie dans le suivi à domicile de la maladie de Parkinson. Congrès JNLF September 2020.
- Virbel-Fleischman C, Houot M, Corsetti E, Rétory Y, Hardy S, Berthelot E, Saverot A, Corvol JC, Roze E, and Grabli D. A monocentric experience of Apomorphine pump follow-up on PD patients: The Optipump Cohort. MDS Congress September 2020.
- Virbel-Fleischman C, Rétory Y, Hardy S, Huiban C, Corvol JC, and Grabli D. User experience of body-worn sensors: perception of patients and health professionals for Parkinson's disease at home follow-up. MDS Congress September 2020.

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List of Abbreviations

%apo: proportion of apomorphine

ABC: Activities-specific Balance Confidence

aDBS: adaptive Deep Brain Stimulation

ADL: Activities of Daily Living

AIMS: Abnormal Involuntary Movement Scale

apo: apomorphine

apoLEDD: LEDD of apomorphine

ASBPD: Ardouin Scale of Behavior in Parkinson's Disease

ASBPD II: part II of the ASBPD

ATT: Attractiveness

BK: Bradykinesia

BKmed: Median of the continuous bradykinesia score

BK75: Third quartile of the continuous bradykinesia score

BK I: Percent of time with bradykinesia at severity level I per periods of 3 hours

BK III+IV: Percent of time with bradykinesia at severity level III+IV per periods of 3 hours

BK Q1: Global first quartile of the bradykinesia score

BK Q2: Global second quartile of the bradykinesia score

BK Q3: Global third quartile of the bradykinesia score

BKS: Bradykinesia Score

BWS: Body-Worn Sensors

COMT-I: Catechol-O-Methyl-Transferase Inhibitors

conv: conventional

convLEDD: LEDD of conventional treatments

CSAI: Continuous Subcutaneous Apomorphine Infusion

DAT: Device-Aided Therapies

DBS: Deep Brain Stimulation

DK: Dyskinesia

DKmed: Median of the continuous dyskinesia score

DK75: Third quartile of the continuous bradykinesia score

DK I: Percent of time with dyskinesia at severity level I per periods of 3 hours

DK III+IV: Percent of time with dyskinesia at severity level III+IV per periods of 3 hours

DK Q1: Global first quartile of the dyskinesia score

DK Q2: Global second quartile of the dyskinesia score

DK Q3: Global third quartile of the dyskinesia score

DKS: Dyskinesia Score

FAB: Frontal Assessment Battery

FDS: Fluctuation Dyskinesia Score

GABS: Gait And Balance Scale

GPI - DBS: Globus Pallidus interna Deep Brain Stimulation

H&Y: Hoehn and Yahr scale

HQ: Hedonic Qualities

HQ-I: Hedonic Qualities - Identification

HQ-S: Hedonic Qualities - Stimulation

HP: Health Professionals

HRQoL: Health-Related Quality of Life

ICD: Impulse Control Disorders

IMU: Inertial Measurement Units

LCIG: Levodopa Carbidopa Infusion Gel

LCLMM: Latent Class Linear Mixed Model

LID: Levodopa-Induced Dyskinesia

LEDD: Levodopa Equivalent Daily Doses

LSVT: Lee Silverman Voice Treatment

MDS: Movement Disorder Society

MDS-UPDRS: Movement Disorder Society Unified Parkinson's disease Rating Scale

MAO-I: Monoamine Oxidase Type B Inhibitors

MEMS: Microelectromechanical systems

MMSE: Mini Mental State Examination

MoCA: Montreal Cognitive Assessment

NMS: Non Motor Symptoms

NMSQuest: Non Motor Symptoms Questionnaire

NMSS: Non Motor Symptom Assessment Scale

PD: Parkinson's disease

PDQ-39: Parkinson's Disease Questionnaire - 39

PQ: Pragmatic Qualities

PTI: Percent of Time Immobile

PTT: Percent of Time with Tremor

QoL: Quality of Life

RBD: REM Behavioral Disorders

REM: Rapid Eye Movement

RGSE: Rating Scale for Gait Evaluation

S&E: Schwab and England Activities of Daily Living Scale

STN-DBS: Subthalamic Nucleus Deep Brain Stimulation

SUS: System Usability Scale

UDysRS: Unified Dyskinesia Rating Scale

UKPDSBB: United Kingdom Parkinson's Disease Society Brain Bank

UPDRS I: part I of the UPDRS

UPDRS II: part II of the UPDRS

UPDRS III: part III of the UPDRS

UPDRS IV: part IV of the UPDRS

UR: User Research

UX: User Experience

var: variation

varApo: variation of apomorphine LEDD

varConv: variation of conventional treatments LEDD

Résumé

Vers l'intégration de l'actimétrie dans la prise en charge de la maladie de Parkinson : perspectives de nouveaux paradigmes de suivi

Le suivi de la maladie de Parkinson (MP) est basé sur un traitement symptomatique de substitution dopaminergique. Celui-ci est ajusté par les médecins tout au long de la vie du patient en fonction de l'évolution des symptômes, mais au stade des fluctuations motrices et des dyskinésies, les adaptations thérapeutiques deviennent plus complexes. Certaines limites dans les moyens d'évaluation actuels ne permettent pas d'obtenir de manière simple une image complète de l'état du patient. Par exemple, leurs entretiens sont subjectifs, les échelles cliniques sont réalisées de façon ponctuelle, et les agendas des patients ont un caractère contraignant. Par ailleurs, les actimètres permettent une mesure objective et continue des symptômes moteurs des patients atteints de la MP en conditions de vie réelle et sans supervision médicale. Leur validité technique pour la détection des symptômes moteurs en temps réel lors d'activités de la vie quotidienne est démontrée. Cette approche peut être utilisée par les neurologues comme support aux adaptations thérapeutiques des patients. L'hypothèse de ce travail de thèse repose sur la perspective de nouvelles stratégies de suivi des patients vers un système en boucle fermée intégrant l'actimétrie. Ce projet apporte un éclairage sur la possibilité d'automatiser la délivrance du traitement par pompe à apomorphine à partir des mesures d'actimétrie en fonction de l'évolution des symptômes. Le premier objectif a consisté à comprendre les effets de l'évaluation des symptômes de la MP sur les adaptations des traitements antiparkinsoniens conventionnels et d'apomorphine dans une cohorte de patients parkinsoniens traités par pompe. L'analyse du suivi longitudinal de cette cohorte a permis de montrer que les évaluations des symptômes par des échelles cliniques expliquent peu les ajustements thérapeutiques opérés. La seconde étude, qualitative, a impliqué des entretiens semi-directifs et des questionnaires

spécialisés afin de considérer l'opinion des patients et des professionnels de santé sur l'actimétrie. Elle a permis de mettre en évidence une bonne expérience utilisateur et une perception positive de trois différents actimètres. Enfin, le troisième travail a été conduit pour évaluer les paramètres d'intérêt dans la lecture des résultats d'actimétrie et pouvant agir sur la décision des neurologues dans les actions thérapeutiques à mener. L'analyse de cas patients virtuels par des neurologues a servi à chercher une correspondance entre leur lecture et leur décision. Cette étude a mis en évidence une lecture équivoque des résultats d'actimétrie dont certains paramètres d'intérêt peuvent influencer les ajustements thérapeutiques suggérés par les neurologues. Dans un contexte où l'actimétrie pourrait assister la prise en charge médicale et satisfaire certaines attentes des patients, les résultats de ce travail suggèrent qu'une standardisation des dispositifs d'actimétrie aiderait à homogénéiser l'interprétation des résultats. De même, les stratégies d'adaptation de la pompe à apomorphine à partir des résultats d'actimétrie pourraient être définies par des règles plus précises. Une automatisation de l'adaptation de la délivrance de la pompe à apomorphine à partir des résultats d'actimétrie nécessiterait d'être étudiée davantage pour faire partie d'un système en boucle fermée. En l'absence d'un algorithme adapté, une étape intermédiaire compatible avec l'état actuel des avancées technologiques consisterait en une boucle hybride. En effet, les spécialistes de la MP pourraient sélectionner les paramètres pertinents parmi ceux proposés par les actimètres. Ces paramètres seraient alors traités par un algorithme développé à partir des décisions thérapeutiques des experts. Ainsi, cette boucle hybride permettrait l'obtention d'un protocole basé sur les décisions des experts, applicable dans un suivi à distance.

Mots clés : Maladie de Parkinson, Actimètres, Suivi ambulatoire, Perfusion sous-cutanée continue d'apomorphine, Stratégies thérapeutiques, Recherche qualitative, Perception, Patients, Professionnels de santé, Système en boucle fermée

Abstract

Parkinson's disease (PD) monitoring is based on symptomatic dopamine replacement therapy, which is adjusted by clinicians throughout the patient's life according to the progression of symptoms. At the stage of motor fluctuations and dyskinesia, therapeutic adaptations become more complex. Some limitations in the current available tools for PD assessment do not allow catching a complete picture of the patient's condition easily. For example, their interviews are subjective, clinical scales are carried out on an *ad hoc* basis, and patient agendas are binding. On the opposite, Body-Worn Sensors (BWS) provide objective and continuous measurement of motor symptoms in PD patients under real-life conditions and without medical supervision. Their technical validity for the detection of motor symptoms in real time during activities of daily living has been demonstrated. This approach can be used by neurologists as a support for patients' therapeutic adaptations. The hypothesis of this thesis work is based on the idea of new patient follow-up strategies with a closed-loop system involving BWS. This project provides perspectives on the automation of the delivery of apomorphine pump treatment from BWS monitoring according to the evolution of symptoms. The first objective was to understand the effects of the assessment of PD symptoms on adaptations of conventional antiparkinsonian treatments and apomorphine in a cohort of parkinsonian patients treated with a pump. The analysis of the longitudinal follow-up of this cohort showed that the assessments of symptoms by clinical scales explain little of the therapeutic adjustments. The second study was qualitative and involved semi-structured interviews and specialized questionnaires in order to consider the opinion of patients and healthcare professionals on BWS monitoring. It highlighted a good user experience and a positive perception of three different BWS. Finally, the third work was carried out to evaluate the parameters of interest in the reading of the BWS results and which may influence the decision of neurologists for therapeutic actions. The analysis of virtual patient cases by neurologists was used to find a correspondence between their reading and their

decision. This study revealed an equivocal reading of BWS results, from which some parameters of interest may influence the therapeutic adjustments suggested by neurologists. In a context where BWS could support medical care and meet certain patient expectations, the results of this work suggest that standardization of BWS would help for results interpretation. Likewise, the adaptation strategies of the apomorphine pump from BWS results could be defined by more precise rules. An adaptive pump delivery from BWS results would need further investigation to be part of a closed-loop system. In the absence of a relevant algorithm, an intermediate solution that would be compatible with the current state of technological advances would consist of a hybrid loop. Indeed, PD specialists could select the relevant parameters among those offered by BWS. An algorithm developed from the therapeutic decisions of the experts would then process these parameters. Thus, this hybrid loop would allow a specialist-based protocol applicable in remote follow-up.

Keywords : Parkinson's disease, Body-Worn Sensors, Ambulatory monitoring, Continuous subcutaneous apomorphine infusion, Therapy strategies, Qualitative research, Perception, Patients, Health professionals, Closed-loop system

1. Introduction

1.1 Parkinson's disease and associated care

1.1.1 General presentation

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease in terms of frequency. PD was initially described in 1817 by James Parkinson in "An essay on the shaking palsy" (Parkinson 1817). He reported on six patients with a slowly progressing disease characterized by "*involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured*". This first description also encompassed some non-motor features that would eventually be re-discovered nearly two centuries later.

In 1872, Charcot finally gave a name to PD and went through the semiology of this age-related disorder. From the 20th century, further discoveries could allow advances in understanding the disease. Nowadays, PD is better known and defined, yet it is still not fully understood. According to current criteria, PD is defined by the association of at minimum bradykinesia with hypertonia or resting tremor (Postuma et al. 2015). These hallmarks of the disease are frequently associated with other motor symptoms such as alterations of gait, posture and speech (so called axial symptoms), and non-motor symptoms (NMS) like autonomic failure, depression, cognitive impairment, sleep disorders, *etc.* (Truong, Bhidayasiri, and Wolters 2008; Khoo et al. 2013).

The main neuropathological characteristic of PD is the loss of dopaminergic neurons in the Substantia Nigra pars compacta (Figure 1), a structure from Basal Ganglia which plays a major role in the regulation of movement (via the nigrostriatal pathway) and executive and

affective processes such as the reward circuit (via the mesocorticolimbic pathway) (Caminiti et al. 2017; Damier et al. 1999).

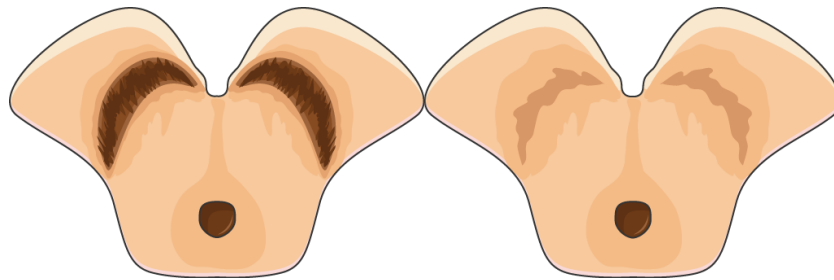


Figure 1: Illustration of the dopamine loss in the Substantia Nigra pars compacta. On the left, black regions show the presence of dopaminergic neurons of a subject without PD, and, on the right, the nucleus has suffered from neuronal death that has decreased the level of dopamine, which is responsible for PD symptoms.

At the early phase of nigrostriatal degeneration, compensation phenomena are put in place, especially with changes in the expression of dopaminergic and non-dopaminergic receptors, and with modifications in the expression of various neuropeptides found in most neurons of Basal Ganglia (Bezard, Gross, and Brotchie 2003).

The other neuropathological feature of PD is the accumulation of alpha synuclein in intracellular inclusion. Alpha synuclein is physiologically present in different parts of the central nervous system and it seems involved in vesicular traffic, synthesis and transport of dopamine, and synaptic plasticity (Baltic et al. 2004). In some specific genetic forms of PD, alpha synuclein is mutated or overexpressed, but accumulation of alpha synuclein is also a major player in the pathophysiology of idiopathic forms of PD. The protein aggregates in the form of intracytoplasmic inclusions called Lewy Bodies, where localization in the tissues are correlated with neuronal death (Spillantini et al. 1997; Dickson 2018). Alpha synuclein disseminates via lysosomal vesicles like Prions, that may play a role in the evolution of the disease (Grozdanov and Danzer 2018).

The first signs of the disease only appear once the neurodegeneration is significant and engenders a critical drop of the striatum dopamine concentration, which creates difficulties in the patient's motion (Cheng, Ulane, and Burke 2010). However, some prodromal symptoms may develop up to 20 years earlier, such as anosmia, digestive or sleep disorders (Postuma et al. 2012; Berg et al. 2015).

1.1.2 Figures

PD is now considered a global burden, having the fastest growth since 1990 among neurodegenerative disorders (Dorsey and Bloem 2017; Dorsey, Elbaz, et al. 2018). In France, 170.000 individuals were treated for PD in 2015 (Moisan et al. 2018), which is in line with the mean prevalence in other occidental countries. However, due to differences in methodologies across countries, institutions and diagnosis criteria, PD prevalence and incidence may vary from one study to another (Muangpaisan et al. 2011; von Campenhausen et al. 2005). Besides, if the projections of Dorsey and colleagues turns out to be correct, we can advocate that more than 6 million individuals are currently affected by PD globally (Dorsey et al. 2007). And, doubtless, this massive increase of the PD population will continue in the next decades (Figure 2), mostly due to the lengthening of life expectancy in the general population and population aging. Furthermore, medical advances may also increase survival and thus result in an even larger increase in patients than expected by 2050 (Rocca 2018).

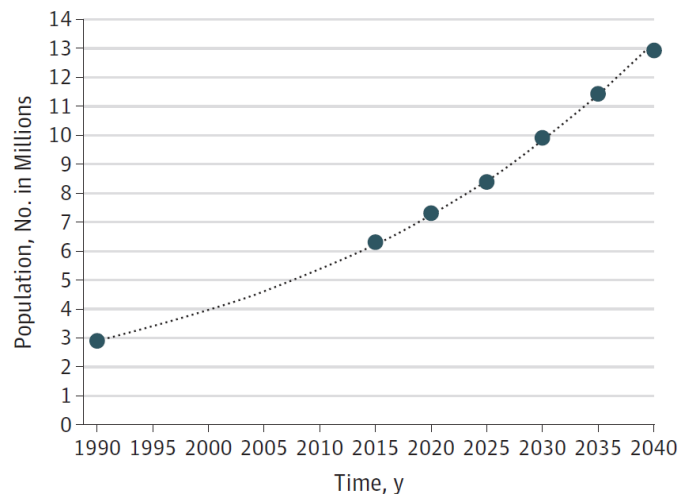


Figure 2: Estimation and projection of the number of patients with Parkinson's disease between 1990 and 2040, according to Dorsey and Bloem 2017

The majority of PD patients are affected by the sporadic form of the disease and only about 5 to 15% of cases are directly caused by dominantly or recessively inherited genetic mutations (Belin and Westerlund 2008). Although PD etiology is still unknown, risk factors have been determined, *e.g.*, environmental factors such as pesticide or solvents (Pezzoli and Cereda 2013), or genetic predisposition (Lesage and Brice 2009). The prevalence of PD is also known to increase with age (Reeve, Simcox, and Turnbull 2014) and is higher in males than in females (Wooten 2004). Physical activity, exposure to tobacco or non-steroidal anti-inflammatory drugs may decrease the risk of developing PD. Since the development of dopa-therapy and the improvement in patients' care, the quality of life in patients with advanced PD has been enhanced in parallel with an increase in life expectancy (Schapira 2007). Unfortunately, mortality among PD patients, particularly for those with early onset is slightly higher than in the general population (Pennington et al. 2010; Ishihara et al. 2007).

1.1.3 Symptoms

The first observable motor signs are generally asymmetric and may appear intermittently (particularly in case of tremor), which can delay diagnosis. Ascertaining a clinical diagnosis of PD often necessitates significant expertise. Red flags that may suggest a differential diagnosis can be counterbalanced by supportive criteria (Postuma et al. 2015). According to the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB), PD diagnosis is based on the clinical evaluation of Parkinsonian hallmarks: akinesia, tremor and muscle stiffness; the exclusion of other Parkinsonian syndromes; and the response to levodopa therapy (Calne 1992).

Motor symptoms

Akinesia is a complex symptom affecting the whole body with slowness of movements (bradykinesia) and difficulties in the initiation of movements and their amplitude (hypokinesia) (Benecke, Rothwell, Dick, and Day 1987; Benecke, Rothwell, Dick, Day, et al. 1987). The movements' disturbances are usually the cause of difficulties in everyday life activities such as taking a shower or buttoning-up a shirt. This disruption of normal actions appears frequently on one side of the body only, the dominant hand showing micrographia (small and illegible handwriting), and sometimes several years before other motor signs of PD. Also, hypophonia (loss of tone voice) or "facial mask" (inexpressiveness of the face) may appear as consequences of akinesia. Other automatic gestures might disappear such as the arm swing while walking or the loss of mimicking during conversation. Akinesia oblige the patient to think about these gestures and the correct execution of movements, making double tasking complex (Benecke et al. 1986).

Stiffness is a combination of abnormal muscle tone and resistance to extension, which engenders difficulties in the execution of passive movements (Lance 1980; Berardelli, Sabra, and Hallett 1983). Muscles are tight and hard on palpation, and a cogwheel phenomenon may

manifest during limb mobilization. Patients may also feel pain, which, together with akinesia, can engender postural distortion and movement disruptions. Stiffness participates in the typical Parkinsonian hunched posture with flexion of the limbs, neck and trunk, favoring bending forward, with increased risk of instability (Andrews, Neilson, and Lance 1973; Mortimer and Webster 1979; Rothwell et al. 1983).

PD tremor can appear in the hands, neck, legs or jaws, and is usually observed at rest (Vaillancourt and Newell 2000). Resting tremor is characterized by regular oscillatory movements of agonists and antagonists muscles at a frequency of 4 to 6 Hz. In the hand, tremor is often described as the “rolling-pill” due to the supination-pronation movement. It is present at the onset of the disease in about 70% of PD patients and is asymmetric (Andrew J Hughes and Lees 1993). Strong emotions, stress or fatigue might increase its occurrence, but actions, either voluntary or passive movements, may stop the tremor. Other forms of tremor may also appear such as postural tremor, at a similar frequency, or tremor of the head, similar to the greater frequency observed in essential tremor.

Apart from the cardinal signs of PD, other motor manifestations are usually observed at a more advanced stage of the disease: postural instability (S. D. Kim et al. 2013), alterations of gait (Nutt, Horak, and Bloem 2011), and freezing of gait (Bloem et al. 2004). These axial signs engender difficulties that increase disability in everyday life, work or social activities. Indeed, patients may experience difficulty in rising from a chair or getting out of a car, and fear obstacles in the outside environment. Gait and balance disorders are frequent in PD patients at an advanced stage but severity and appearance varies among patients. Such symptoms are still poorly addressed in terms of medical and/or surgical treatments (Benatru, Vaugoyeau, and Azulay 2008). Postural instability in PD is characterized by the loss of balance reflexes, which can lead to falls (Crouse et al. 2016). Gait disorders are the expression of akinesia and stiffness but other mechanisms including brainstem and cortical dysfunction are involved (Grabli et al.

2012; Weiss et al. 2020). Hypokinesia creates small and shuffling steps, the coordination of steps is dysfunctional which can modify cadence and diminish speed compared to subjects without PD (Williams, Peterson, and Earhart 2013; O’Sullivan et al. 1998; Mak 2013).

The freezing of gait (FoG) is identified as trampling steps especially at the initiation of gait or when crossing narrow passages (Bloem et al. 2004). FoG is characterized by immobilization when walking, and is often associated with postural instability when PD progresses. Suddenly, the step sequence is interrupted for a few seconds and the walk cannot be initiated or continued despite intention (Nutt et al. 2011; Giladi and Nieuwboer 2008), which may engender falls. Indeed, the legs can alternatively shake at a 3 to 8 Hz frequency, at the same time of a cadence increase and a decrease of step length (Moore, MacDougall, and Ondo 2008; Alice Nieuwboer et al. 2001). As the feet and toes barely leave the ground, patients commonly feel being glued to it. FoG generally appears at an advanced stage of the disease (Panisset 2004) but in less than one third of the cases, it can be present during the first years of the disease. FoG is then expressed with low severity and during short episodes, which can make one think about an hesitation mark in the patient’s action (Tan et al. 2011). At this early stage, FoG can be addressed efficiently with treatment, however, therapy is less effective in advanced stages (Gao et al. 2020).

As a result of dopaminergic neurons loss and non-physiological stimulation of dopamine receptors by conventional anti-Parkinsonian treatments, so-called motor complications including fluctuations and dyskinesia occur. Levodopa-induced motor complications limit many patients in their daily life (Olanow, Calabresi, and Obeso 2020). Fluctuations between ON and OFF states can be significantly disabling, making the patient alternatively experience normal and bad moments periods in the same day. To some extent, fluctuations may be complicated by hyperkinetic involuntary movements, named Levodopa-Induced Dyskinesia (LID). The risk of LID increases in patients with a young onset, high exposure to dopa-therapy

and greater severity of the disease (Thanvi, Lo, and Robinson 2007). LID can be classified according to appearance in relation to levodopa intake (Figure 3).

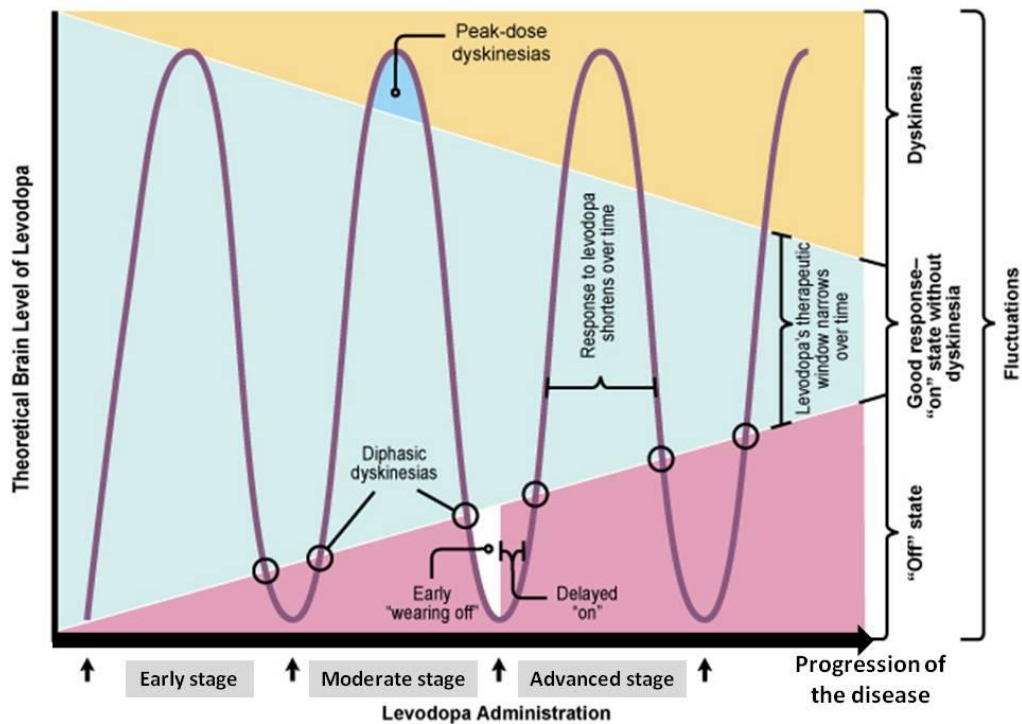


Figure 3: Representation of LID and fluctuations between OFF and ON states according to levodopa intakes and the disease evolution

As the disease progresses, the effect of levodopa therapy is delayed (“delayed on”) and shortened (“early wearing-off”), which can engender diphasic dyskinesias. Also, peak-dose dyskinesia may appear while levodopa doses are not bigger. The window of therapeutic action (ON state) becomes narrower, OFF state and ON state with dyskinesia become more important and frequent. Image taken from Project In Knowledge 2017, Parkinson’s disease Edition: Early Diagnosis and Comprehensive Management (Chapter 5), Robert A Hauser.

First, peak-dose dyskinesia are the most common forms, and appear when the plasma concentrations of levodopa are the highest. The reduction of levodopa doses and amantadine may improve peak-dose dyskinesia (Ory-Magne et al. 2014). Second, diphasic dyskinesias appear just after or just before the levodopa intakes and are sometimes described as onset and end of dose dyskinesia. They are usually characterized by painful dystonic movements

(contractions of the muscle making the limb twist in an uncomfortable position), frequently involving the legs. Finally, OFF dystonia may occur in the early morning, before the first treatment dose intake. The unpredictability of some LIDs is complex to treat and very debilitating in everyday life actions. Fluctuations not only affect motor symptoms of PD, but also NMS, neuropsychiatric symptoms such as mood or fatigue, the autonomic function, through dysregulation of the sweating or the gastrointestinal circuitry, and sensory aspects (Aquino and Fox 2015).

Non-motor symptoms

A very large spectrum of non-motor symptoms (NMS) is described in PD, but vary among patients and in terms of severity and time of onset. As such, treatment management is challenging (K Ray Chaudhuri, Healy, and Schapira 2006). The most common are dysexecutive syndromes like apathy (Pluck and Brown 2002; Oguru et al. 2010), cognitive or psychiatric troubles such as depression or dementia (Aarsland et al. 2012), or dysautonomia (Poewe 2007; Goldstein 2003), fatigue or sleep disorders (Comella 2007; Kumar, Bhatia, and Behari 2002; Bhidayasiri and Trenkwalder 2018). Cognitive problems can be observed in PD patients at an advanced stage of the disease, and do not respond well to available levodopa treatment. About one third of PD patients are diagnosed with dementia (Aarsland, Zaccai, and Brayne 2005), and this more than doubles after 10 years (Aarsland 2003). Cognitive decline, in addition to motor symptoms, is one major disabling factor for loss of autonomy. Origin is likely multifactorial and linked to the spread of synucleinopathy to other brain areas together with the synergistic role of additional pathologies (beta-amyloid or tau for instance) (Coughlin, Hurtig, and Irwin 2019). Sleep disorders are also prodromal signs in PD and occur during the rapid eye movement sleep phase (REM). Patients with REM behavioral disorders (RBD) express involuntary behavior that can be surprising and even violent during their dreams. RBD are due to the loss of muscle atonia that normally accompanies this sleep phase (Postuma et al. 2006).

Evolution

The progression of the disease comprises two main axes: (i) as dopaminergic loss continues, the response to dopaminergic drugs will eventually change over time leading to fluctuations and dyskinesia, and (ii) as the synucleinopathy spreads over the brain, levodopa unresponsive symptoms, NMS frequency and severity increase. The balance between these two phenomena is variable across individuals. However, early onset disease is associated with earlier fluctuations and dyskinesia, but a less severe disease course overall (Schrag et al. 1998). Conversely, late onset, axial symptoms and a high load of non-motor features favor rapid progression towards loss of autonomy (Fereshtehnejad 2015; Lau et al. 2019).

The first phase after diagnosis, called the “honeymoon”, is commonly well managed by dopamine replacement therapy and can last for several years (Cesaro and Defebvre 2014; Erro et al. 2016). Five to eight years after treatment onset, patients experience motor and non-motor fluctuations, and treatment-induced involuntary movements. The degree of disability differs in patients and their socio-professional activities may be affected to varying intensities. Moreover, the occurrence of symptoms may depend on each patient and their perception of those symptoms also plays a role in the patient’s global state.

1.1.4 Assessment of symptoms

The assessment of PD symptoms is mainly based on examination of the patient. Experts observe patients during visits or hospitalizations and can use different tools to support their conclusions. These tools include scales, validated questionnaires, either answered by the patient or by the clinician’s auscultation, patient interview, and a patient diary.

A large variety of scales supports the assessment of PD symptoms to define a diagnosis, evaluate progression, or quantify severity (Ebersbach et al. 2006). They can be general or

targeted in one domain applied to PD. Given the high number of scales used in PD, only the most relevant to this work are considered here.

The Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a revision of the UPDRS, which was developed with the intention of making common assessments in clinical studies (Fahn, S., & Elton, R. L. 1987). The MDS-UPDRS is divided into 50 items and four subscales related to the different domains of PD: the first part is related to behavior and mood (MDS-UPDRS part I), activities of daily living are assessed by the patient answering an auto-questionnaire in the second part (MDS-UPDRS part II), the third part is linked to motor examination after realization of movements according to detailed instructions (MDS-UPDRS part III), and the fourth part assesses complications linked to dopa-therapy (MDS-UPDRS part IV) (Goetz et al. 2007). Each item scores from 0 (normal) to 4 (severe) to arrive at a global quantitative score. This scale is the most widely used by neurologists to evaluate PD symptoms in the research setting (Bhidayasiri and Martinez-Martin 2017).

The Hoehn and Yahr scale (HY) judges the state of PD by describing the progression of symptoms (Hoehn and Yahr 1967; Goetz et al. 2004). The HY scale places the patients in one of five stages depending on motor impairment severity and disability. It is included in the MDS-UPDRS IV and can be performed in both ON and OFF states.

Other scales may focus on the evaluation of specific symptoms. For example, the Abnormal Involuntary Movement Scale (AIMS) can be used to assess therapy-induced motor complications by rating the severity of dyskinesia. The Unified Dyskinesia Rating Scale (UDysRS) evaluates the appearance of dyskinesia in the last past week in four parts (Goetz, Nutt, and Stebbins 2008). The impairment of gait can be judged via the Rating Scale for Gait Evaluation (RGSE) (P. Martinez-Martin et al. 1997) or the Gait And Balance Scale (GABS), which was validated as an easy-to-use tool with high reliability for assessing functional impairment associated with abnormalities in gait and balance (Thomas et al. 2004). The FoG

Questionnaire was validated with high test-retest reliability to effectively screen the presence of FoG in PD patients (Giladi et al. 2009). Mobility and fall risk can be screened with the Tinetti Mobility test (Kegelmeyer et al. 2007). Finally, the Activities-specific Balance Confidence (ABC) scale was designed to detect loss of balance confidence, and allows the evaluation of difficulty perceived in the completion of activities both indoors and outdoors, including the fear of falling in Activities of Daily Living (ADL) (Myers et al. 1998; Powell and Myers 1995).

The interview-based Schwab and England Scale (SE) is used to assess capabilities in ADL and the degree of functional independence of patients in ON and OFF states (Schwab and England 1969; McRae 2000). Cognitive functions and memory abilities are tested via the Mini Mental State Examination (MMSE) (Folstein, Folstein, and McHugh 1975) and the Frontal Assessment Battery test (FAB) (Dubois et al. 2000). Cognitive impairment can also be evaluated with the Montreal Cognitive Assessment (MoCa), which is a short screening tool for the cognitive domains of executive and visuospatial function, memory, language and attention (Gill et al. 2008). In parallel, MDS proposed recommendations for a robust diagnostic in the five domains of cognition (attention/working memory, executive function, language, memory, and visuospatial function) with at least two tests (Goldman et al. 2015). Dementia in PD patients may be detected with full neuropsychological testing as the suggested procedure of MDS (Barton et al. 2012). Quality of Life (QoL) is often assessed by the PDQ-39 scale, or PDQ-8 (Peto et al. 1995; Auquier et al. 2002) which explore the difficulties caused by PD in relationships, social situations and communication. The Ardouin Scale of Behavior in Parkinson's Disease scale (ASBPD) provides assessment of depression, anxiety, apathy, impulse control disorder, dopaminergic dysregulation, psychosis, and emotion control disorder (Ardouin et al. 2009). Especially, the second part of ASBPD is related to apathy. A broad range of NMS can be assessed with the Non Motor Symptoms Questionnaire (NMSQuest), which is a patient-based questionnaire composed of 30 items grouped in nine domains of non-motor

symptoms (Kallol Ray Chaudhuri et al. 2006). The Non Motor Symptom Assessment Scale (NMSS) is a rater-based scale composed of 30 items (K Ray Chaudhuri et al. 2007). Few validated scales exist to assess specific symptoms of the long list of dysautonomia manifestations (Evatt et al. 2009) .

Though validated by clinical trials in most cases, these scales are limited because of their *ad-hoc* realization, which does not provide an image of changes in time, while the evolution of symptoms is crucial for the evaluation of PD. Other scales use a retrospective approach (MDS-UPDRS part IV, for example) that relies on a patient interview.

In a more subjective assessment of symptoms, a patient diary allows the self-classification of the patient's state into several categories with a prospective approach. Different types of diary have been validated against the clinical evaluation of PD experts, but they usually have in common a structured report of OFF state, ON state with or without dyskinesia, or asleep, in periods of 30-minutes during a few days at home. According to the authors, the OFF state can be further subdivided into OFF and partial OFF states (Reimer 2004), dyskinesia can be troublesome or not (R. A. Hauser et al. 2000), and the ON time may include dyskinesia or not. Thus, good times are defined by patients as ON time without dyskinesia or ON time with no troublesome dyskinesia, and bad times as OFF time or ON time with troublesome dyskinesia. Currently, the patient diary is considered the “gold-standard” for evaluation of PD motor complications (Robert A. Hauser, Deckers, and Leher 2004).

1.1.5 Anti-Parkinsonian therapies

To date, there is no curative treatment for PD, and the current strategy is to provide the substitution of dopamine by means of several symptomatic therapies. The reference drug used in PD is levodopa (S. H. Fox et al. 2011; 2018). It is the immediate precursor of dopamine, and is able to cross the blood-brain barrier, and boosts the biosynthesis of dopamine, which is no

longer present in large enough quantities due to the neuronal loss. Levodopa allows the recovery of dopaminergic activity with good benefits (The Parkinson Study Group 2004; Kakkar and Dahiya 2015) and is always associated with the levodopa decarboxylase inhibitor (either carbidopa or benserazide) in order to reduce peripheral side effects (orthostatic hypotension, nausea, *etc.*) and to improve its bioavailability in the brain (Rinne and Molsa 1979). However, at some point and due to the pulsatility stimulation of dopamine receptors and due to the progression of neuronal loss, levodopa intake can engender adverse effects over the long term, with effects such as fluctuations and dyskinesia (Rascol et al. 2003; Obeso, Olanow, and Nutt 2000). After 4 to 6 years of levodopa therapy, more than 40% of the patients trigger these motor complications that can remain out of control (Ahlskog and Muentner 2001). Complications follow the fluctuating efficacy of the antiparkinsonian treatment pharmacology between ON and OFF phases, and dyskinesia are directly linked to the intake of levodopa. The other main therapeutic class for PD treatments are agonists of D2 dopamine receptors. In comparison with levodopa, starting the treatment with a dopamine agonist delays the occurrence of dyskinesia (Rascol et al. 2000).

Impulse control disorders (ICD) like addictions to game, food or sex, daytime sleepiness, hallucinations, or aggressiveness are specifically associated with the cumulative dose of dopamine agonists (Corvol et al. 2018; Weintraub et al. 2010). Various strategies can be organized with conventional treatments, mainly shortening the time interval between levodopa intakes, or acting on its pharmacokinetics. Clinicians can combine several therapeutic solutions and adjust doses and the number of intakes according to the patient's motor and non-motor symptoms. In addition to the direct stimulation of dopaminergic receptors by provision of dopamine agonists, the dopamine metabolism can be reduced via enzymatic inhibitors. Thus, to potentiate its action, levodopa can be accompanied by Monoamine Oxidase Type B (MAO-B) or Catechol-O-Methyl-Transferase (COMT) inhibitors (Schapira 2007). They either

decrease the time in OFF or increase the time in ON. Other specific molecules may be prescribed in particular cases. For example, anticholinergics are mostly useful for tremor and in young patients, and amantadine or clozapine are solutions provided to reduce dyskinesia (S. H. Fox et al. 2018).

However, the various combinations of conventional therapy may not be enough to stabilize the symptoms. Then, second line therapies may be considered by the medical team to provide a continuous effect (Olanow, Calabresi, and Obeso 2020). The solution is implemented in device-aided therapies (DAT), which are available in three types: deep-brain stimulation (DBS), Levodopa-Carbidopa Intestinal Gel (LCIG), and Continuous Subcutaneous Apomorphine Infusion (CSAI) (Figure 4). They all have been proven to be effective to reduce fluctuations and dyskinesia, and improve QoL (Deuschl et al. 2006; Olanow et al. 2014; Fernandez et al. 2015; Weaver 2009; Katzenschlager et al. 2018).

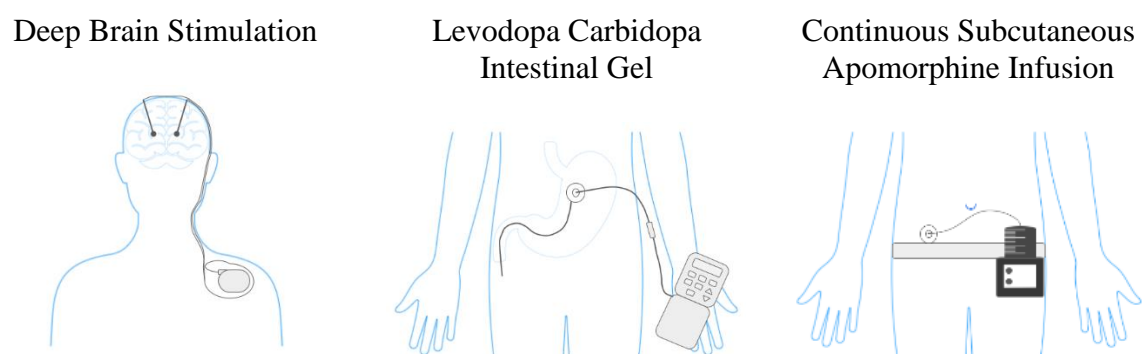


Figure 4: Illustrations of the three DAT options

First proposed in the 1980's, DBS is based on the bilateral implantation of electrodes in the brain to continuously stimulate a specific nucleus of the Basal Ganglia at high frequency (Benabid 2003). The Subthalamic Nucleus (STN) and the Globus Pallidus interna (GPi) are efficacious targets of DBS for PD (Kringelbach et al. 2007; Weaver et al. 2012). STN-DBS improves both akinesia, hypertonia and tremor, and allows a reduction of dopaminergic drugs doses by 50% (Deuschl et al. 2006). Less frequently used in PD, GPi-DBS's main effect is an

improvement of LID while dopaminergic doses will remain unchanged (Rodriguez-Oroz 2004; Rodriguez-Oroz, Moro, and Krack 2012). Finally, DBS of the Vim nucleus is sometimes used in patients with tremor dominant PD that are not eligible to STN-DBS. Leads implantation is performed according to a stereotaxic procedure, a neurosurgery technique with extreme precision (Welter et al. 2014). The benefits and side effects are tested in the operative room while the patient is awake, allowing higher precision for the leads placement. The neurologist sets up the stimulation parameters during the following days with an implanted pulse generator (a small battery-operated device placed under the skin in the clavicular region and connected to the leads). While clinical benefits have been validated, DBS remains an invasive approach, and the benefit-to-risk ratio has to be considered for each patient (Weaver 2009). DBS might not provide sufficiently beneficial results in some patients, and the surgery and the stimulation may engender adverse events. Accordingly, selection of eligible patients is strict, and only a few PD patients have this surgical option (Lang and Widner 2002; Pollak 2013). For STN-DBS, selection criteria are well defined and include severe PD in patients below age 70, link to a persistent resting tremor, uncontrolled by medication, and/or presence of motor complications due to levodopa therapy, such as fluctuations and dyskinesia, despite optimized treatment management. Axial signs that do not respond well to DBS are contraindications, as well as cognitive problems because they are predictors of poor results (Welter et al. 2002). DBS at an early stage of the disease increases QoL and reduces impact on the socio-professional sphere while the disease progresses (Schupbach et al. 2007).

Another DAT option is the continuous delivery of levodopa via intestinal infusion, or LCIG. A carbidopa-levodopa gel is distributed percutaneously through a trans-gastric jejunostomy device, which decreases fluctuations of levodopa plasma levels. LCIG has been proven efficient in advanced PD patients and can reduce OFF time and increase ON time with troublesome dyskinesia (Olanow et al. 2014; Antonini et al. 2016). QoL is also improved with LCIG

(Fernandez et al. 2015) but some primary safety concerns may occur, especially due to the system (Dag Nyholm 2012).

Finally, the third DAT option is the continuous subcutaneous delivery of apomorphine. Apomorphine has a short half-life, is highly lipophilic with a strong first-pass metabolism dopamine agonist on D1 and D2 receptors. This profile explains why apomorphine is administered continuously and subcutaneously. CSAI is programmed with specific flow rates and dedicated periods of delivery of the pump depending on the patient's symptoms and life habits. CSAI is an interesting solution for advanced PD patients, and it has been proven efficient to reduce time in OFF, dyskinesia, and improve quality of life (Katzenschlager et al. 2018; Colzi, Turner, and Lees 1998; García Ruiz et al. 2008; Manson, Turner, and Lees 2002; Di Rosa et al. 2003; Pietz, Hagell, and Odin 1998; Katzenschlager et al. 2005; Drapier et al. 2016). Still, side effects may appear and have to be carefully controlled (Senek and Nyholm 2014). The most common adverse events are skin nodules, nausea, orthostatic hypotension, hallucinations, impulse control disorders, sleepiness and confusion. Drug tolerance to apomorphine is evaluated rigorously during the first days of initiation with CSAI, and safety and efficacy are regularly monitored at the occasion of standard follow-up and/or dedicated inpatient visits. Among others, the choice of the DAT option depends on the benefit-to-risk ratio, to best improve symptoms and avoid as much as possible side effects according to a patient's profile (P. Odin et al. 2015; Dijk, Espay, and Katzenschlager 2020).

The management of PD involves a multidisciplinary approach, consisting of medical therapy and non-medication solutions to consider all the impacts of PD on the patient's life (Rajan et al. 2020). Indeed, the effectiveness of various complementary interventions has been studied in the literature in the previous years with clinical trials (Bloem, de Vries, and Ebersbach 2015). Physiotherapy, acupuncture, Tai Chi, Qi Gong, Yoga, or even Cannabis, have been highlighted with promising benefits for PD patients (Deuel 2020; Cosentino et al. 2020;

Yitayeh and Teshome 2016). Occupational therapy in its variety of approaches may also lead to an improved QoL (Tofani et al. 2020). Physical activity may be an advantage for PD patients to modify the evolution of symptoms (Amara et al. 2019) and could be part of a rehabilitation program to improve balance dysfunction or postural instability (Yitayeh and Teshome 2016), and freezing of gait (Cosentino et al. 2020). Additionally, dance and music therapy are also innovative approaches to consider for enhancing gait and cognition (A. P. S. Pereira et al. 2019). Moreover, a specific voice training program, the Lee Silverman Voice Treatment Loud (LSVT Loud®) is now often used to improve speech and facilitate communication for PD patients, and even to work on mobility (LSVT big®) (C. Fox et al. 2002; 2012).

1.1.6 Context of care

Currently, access to care for PD patients is not equivalent from one country to another. However, the growing number of patients undoubtedly marks the need for advances in PD management to avoid an out-of-control burden in the next decades (Gustavsson et al. 2011). The contribution of neurological disorders, and especially PD, in daily-life disability is well-established (Dorsey, Elbaz, et al. 2018). The increasing aging of the population and life expectancy of PD patients contributes to the growing need for expertise in neurological conditions (Feigin et al. 2017; Wanneveich et al. 2018), and also to methods to stem the rising costs associated with PD. Moreover, there are considerable indirect costs due to the inactivity of a number of patients and the involvement of the family in PD management. Further, PD entails implications of several healthcare delivery systems, which engenders important direct medical costs (Huse et al. 2005; von Campenhausen et al. 2011). For instance, in the United States, in 2010 the economic impact of PD was estimated at \$14 billion, and indirect costs \$6 billion (Kowal et al. 2013). Moreover, the costs related to PD tend to increase with disease progression (Dahodwala et al. 2020). In France, despite a specific organization of the health

system, PD is also a costly disorder (LePen et al. 1999). Non-medical expenses are another cost, such as dedicated household furniture due to the loss of autonomy in PD patients, and the need for nursing home care (Huse et al. 2005; Oguh and Videnovic 2012). The institutionalization of patients in long-term care facilities due to care needs or safety concerns also accounts for PD expenses (Tison et al. 1997; Abendroth, Lutz, and Young 2012; Bjornestad et al. 2016). Thus, PD is a major public health cost and the need for healthcare services is significant (Parashos et al. 2002). Unfortunately, a number of patients do not see a specialist because the need often exceeds the supply (Dorsey and Bloem 2017). Moreover, movement-disorders specialty centers follow only a few PD patients (Antonini et al. 2018). In the meantime, disease complications like dyskinesias have an impact and increase healthcare costs and lead to a poor quality of life for patients (Pechevis et al. 2005). This situation emphasizes the need of original paradigms of care, which could improve the quality of follow-up in a context of limited resources.

1.2 Current PD care adaptation from a systematic point of view

1.2.1 PD patient follow-up

Generally, PD patient follow-up occurs during outpatient visits, as inpatient stays at the hospital are uncomfortable for patients and costly (Oguh and Videnovic 2012). However, outpatient visits may not be the ideal way to evaluate the variety of PD symptoms. Indeed, several pitfalls need to be taken into account when observing a patient during consultation.

For example, interactions between physicians and patients are short and *ad-hoc*, and they do not allow the observation of fluctuations across time. Visits are also typically distant, and appointments are usually every six to twelve months when the disease is well managed. Shorter delays can be applied when detailed follow-up is needed, but the burden of physicians and hospitals may make changes to appointment availability difficult. To the very best of our knowledge, there is no validated scheme of meetings between the patient and the medical team.

Various plans may be programmed depending on the various centers and patients' profiles. This non-continuous follow-up may be an obstacle to optimal PD management.

Moreover, the medical environment can disturb the natural behavior of patients. For instance, FoG has been demonstrated to be context- and mood-dependent. FoG is often triggered in narrow spaces and when walking or turning between chairs and while maneuvering through obstacles in a typical home environment (Schaafsma et al. 2003). Clinicians can try to replicate this type of situation at the hospital, but FoG may also be affected by the fact of being observed (Alice Nieuwboer et al. 1998), and gait is frequently improved during the visits. Indeed, the “white-coat effect” is a delicate phenomenon that engenders social anxiety on the patient due to the clinical evaluation (Geh et al. 2011), and by consequence might modify the appearance of symptoms and the behavior of patients during a clinic visit. Furthermore, the visit conclusion is mainly based on a patient interview, which can be biased by various elements. First, the degree of freedom in the discussion between the patient and the physician might be a factor. Second, patients may experience flawed recall of symptoms due to memory loss or difficulties in remembering symptoms progression. Also, sensibility to symptoms may be impacted by the slow progression of PD. Third, patients and clinicians might think in different frameworks regarding the definition of symptoms. Indeed, as an example, patients may get tremor and dyskinesia mixed up. Differences have been shown in the self-evaluation of symptoms by patients and the assessment by clinicians (Shulman et al. 2006). As such, the assessment of PD symptoms in an ecological environment without medical supervision might be an advantage.

Clinical rating scales are also used in the follow-up of patients. However, they may be time consuming and cannot reflect fluctuations in symptoms because of the nature of their execution, and depend on the evaluator's expertise. PD assessment by scales might not be replicable in varied environmental conditions (Bhidayasiri and Martinez-Martin 2017), and sometimes there is no universally-agreed rating scale for recording a specific symptom (Thanvi, Lo, and

Robinson 2007). Finally, the current gold-standard in the appraisal of fluctuations or dyskinesia duration and burden is the patient diary (Robert A. Hauser, Deckers, and Leherter 2004; R. A. Hauser et al. 2000). However, compliance in filling the diary decreases over time and recall bias and diary fatigue are common problems of diary use (Papapetropoulos 2012). In real-life situations, diary filing may be delayed in the day because of its cumbersomeness, or caregivers may fill in the diary instead of patients. Moreover, patients may need significant to be able to accurately record ON and OFF times (Goetz et al. 1997). In addition, patients with impaired communication may undergo the same difficulties in filling the diary as during an interview. As such, there are still many limitations even with this gold-standard, making its use infrequent in clinical routine. A more objective evaluation of symptoms may help reduce the risks of human variability in PD management (Klucken et al. 2015).

There is an essential need for other solutions that provide a reliable assessment of PD even in complex cases and without multiple inpatient or outpatient visits. A possible approach is to adopt a continuous evaluation of symptoms and their fluctuations in real-life situations, with a non-invasive and ergonomic tool. Such a solution can utilize body-worn sensors (BWS) for continuous, objective and real-life monitoring of motor symptoms.

1.2.2 Objective monitoring

Objective monitoring allows for quantitative and continuous assessment in real-time or remotely of symptoms or physiological parameters. Physiological measures are widely used in numerous clinical applications to manage specific disease conditions. They may be employed in various situations, either for wellness monitoring, diagnosis of disorders, assessment of treatment efficacy, safety monitoring, or home rehabilitation (Shyamal Patel et al. 2012). Such monitors already provide tremendous diagnostic value in the quantitative evaluation of diabetes (Villena Gonzales, Mobashsher, and Abbosh 2019), heart and respiratory issues (Porges and

Byrne 1992). Current monitors can assess blood pressure, blood oxygen saturation (Kong et al. 2013), *etc.* Technical solutions that involve monitors may involve inpatient hospitalization, a relatively short examination in clinical or laboratory settings, or at home follow-up.

Stationary systems afford accurate data about PD motor symptoms in laboratory settings. Examples include optoelectronic systems with a 3D-camera that allows capture of complete body motion and position through markers placed on the body with information captured via infrared cameras recording at a high frequency and high resolution the displacement and position of markers positioned on the body (Das et al. 2011). Tri-dimensional trajectories of movements are then analyzed with sophisticated software and enable the interpretation of task performance (Morris et al. 1999; Merriaux et al. 2017; McCandless et al. 2016). Instrumented walkways (such as the GAITRite system; CIR Systems Inc, Clifton, NJ, USA) are laboratory-based techniques that can contribute to detailed spatial and temporal analysis of PD motor symptoms, gait analysis, locomotion or balance by measuring ground reaction forces during walking (Chien et al. 2006; Chastan et al. 2008; 2009). Another way to quantify movement in PD is to use electromyography that captures electrical activity generated by muscles (Ruonala et al. 2018). This technique is useful for measuring muscle activity, especially when muscles are affected by a disorder, like severe weakness. However, it involves a cumbersome setup procedure and can hinder the normal movements of a patient. The previously cited instruments are useful in research and the data they provide furthers an understanding of PD mechanisms. However, such instrumentation is expensive and requires expert operation and maintenance, which limits their use to a number of specialty centers. Moreover, despite having validated accuracy, these measurement techniques require strict protocols during movement evaluation and they are necessarily performed in research or clinical settings, and only represent a glimpse of a patient's life. Thus, while they contribute to an objective and accurate assessment of PD motor symptoms, these systems are unable to provide ambulatory evaluation of PD parameters

in daily life (Fu and Mo 2018). Another consideration is that standardized settings may provide relatively limited information on PD motor symptoms since characteristics of movements and behaviors in laboratory settings differ from those in naturalistic environments (Son, Park, and Kim 2018).

More easy-to-use systems have been developed to objectively quantify human movements (Chen et al. 2016). Wearable accelerometry-based devices were introduced in the late 20th century to measure physical activity (Johansson, Malmgren, and Alt Murphy 2018). This development has been enabled by the miniaturization of sensors with microelectromechanical systems (MEMS) technology, which has reduced the size and cost of inertial measurement units (IMU) consisting of accelerometers and gyroscopes (Shyamal Patel et al. 2012; Sprager and Juric 2015; Godwin, Agnew, and Stevenson 2009). Their size, amplitude range, sampling frequency, sensitivity and accuracy may vary, which can engender differences in performance. Thus, it is important to consider IMU specifications to ensure consistency in the intended measure (Monje et al. 2019). The growing number of embedded computers surrounding our daily activities has facilitated the application of IMU to healthcare (De Venuto and Sauter 2018). Technologies have matured in the last fifteen years, becoming more sophisticated thanks to advances in computing power and mass data storage, as well as via machine learning algorithms and internet-enabled information accessibility (Kubota, Chen, and Little 2016). Sensors have become unobtrusive and cheap, and they can be attached to any body part and offer prolonged periods of monitoring that can be done under ecological conditions (Maetzler et al. 2013). These sensors can be worn on the body and used unobtrusively with routinely performed movements to record typical information on movements (orientation, amplitude, frequency), and can also translate this information into a type of activity like gait, posture transition, or the PD cardinal signs (Rovini, Maremmani, and Cavallo 2017). Numerous studies already suggested with technical validation that Body-Worn

Sensors (BWS) are able to accurately measure PD motor symptoms in a daily-life context (Rovini, Maremmani, and Cavallo 2017), such as they may influence therapeutic decisions and the resulting outcomes (Maetzler, Klucken, and Horne 2016). Indeed, the current options for quantitative assessment of PD symptoms via continuous monitoring in real-life conditions with ergonomic BWS have been analyzed, classified and described in a number of reviews in the field (Sánchez-Ferro et al. 2016; Rovini, Maremmani, and Cavallo 2017; Ramdhani et al. 2018; C. R. Pereira et al. 2019; Ossig et al. 2015; Monje et al. 2019; Maetzler, Klucken, and Horne 2016; Hobert et al. 2014; Maetzler et al. 2013; Kubota, Chen, and Little 2016; Johansson, Malmgren, and Alt Murphy 2018; Godinho et al. 2016; Ahlrichs and Lawo 2013; Teshuva et al. 2019; Silva de Lima et al. 2017; Dobkin and Martinez 2018). Authors generally agree on the advantages that BWS could have for PD care management. Apart from the expansion of knowledge in PD symptoms for research purposes, BWS may be useful in the long-term follow-up of patients (Pan et al. 2013; Demonceau et al. 2015). Compared to current evaluation tools, BWS may have advantages in assessing the quality of movements, assisting in rehabilitation, evaluating the outcomes of treatment, or for supporting the differential diagnosis of PD patients (Hobert et al. 2014). BWS may measure with effectiveness and reliability physical activity and mobility, akinesia, tremor, gait impairment, postural instability, dyskinesia and fluctuations (Maetzler, Klucken, and Horne 2016; Sánchez-Ferro et al. 2016). Moreover, the possibility of access to continuous and real-time objective data may enhance the expertise of clinicians on a specific patient. Also, perhaps, the patient's engagement may be enhanced by the potential visualization of their own disease picture. However, a variety of outcomes can influence the quality of clinical evidence and consequently clinical decision-making. Several researchers have noted the methodological heterogeneity of technical validation methodology and outcome measures (Belić et al. 2019; Lindemann et al. 2014; Monje et al. 2019; Kubota, Chen, and Little 2016; Fu and Mo 2018; Son, Park, and Kim 2018). Besides sensor specifications that may

differ, the position of the BWS on the body diverge according to development criteria and symptom assessed (D. W. Kim et al. 2019; Hubble et al. 2015). Moreover, machine learning techniques behind algorithms that allow the detection of PD symptoms are diverse (Belić et al. 2019; C. R. Pereira et al. 2019; Ramdhani et al. 2018), and the presentation of results may not be the same (Silva de Lima et al. 2017). Despite the many advantages BWS can provide to PD management, their integration into clinical practice depends on user acceptance. Nonetheless, continuous and real-life monitoring also raises privacy concerns about the collected personal health data. Mature technology for objective monitoring in PD is available and may answer the needs of a more complete and unbiased follow-up of patients. An increasing number of BWS are still being validated to assess PD related signs. Overall, the clinical applications of BWS and enhancement of PD care due to major technological advances are promising.

1.2.3 Closed-loop systems

The monitoring of any parameter of interest in normal health, or acute or chronic disease may lead to its modification by a human action or a machine, live or remotely, in order to make it correspond to a reference. Recent advances in medical devices, via electronic and algorithmic development, miniaturization, and growing acceptance in the general population and among medical professionals, have made feasible improvements in follow-up care. Research and development teams now aim to produce very sophisticated systems to facilitate a patient's life and a caregiver's work. Such systems include closed-loop systems.

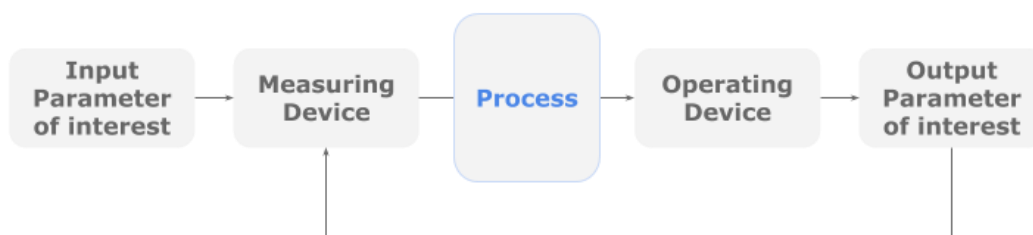


Figure 5: Scheme of a general closed-loop system.

A closed-loop system includes a set of devices that automatically regulates a process in the system to make it conform to a reference state or value, without human interaction. A closed-loop system may be composed of elements involved in the operative structure, *i.e.*, measurement and operating devices that respectively monitor the parameter of interest and act on it, and intelligent systems, where an algorithm processes data and determine an action (Figure 5). Here, we consider the possibility to get closed-loop systems in PD by looking at examples of other systems in healthcare.

Closed-loop devices that may apply for PD involves the patients, and more precisely their symptoms, include a medical device for symptom monitoring, and another component to provide an action to influence the symptom until it matches a target. Personalized treatments are fundamental to achieving the best possible outcomes in chronic diseases (Bhidayasiri et al. 2020) and a PD closed-loop system would allow dynamic actions that are closely individualized to a patient's particular PD symptoms. Currently, the management plan of PD patients pursues an "open-loop" system that necessitates multiple back and forth interactions for evaluations and actions, and, then, several outpatients or inpatient visits. There is a long way to go towards achieving optimal therapeutic efficacy over many weeks or even months (Bronstein et al. 2011). Indeed, for other medical conditions, the automatic adaptation of therapy outcomes according to the measurement of patients' inputs already exists, for instance, diabetes, sleep apnea and ventilation. In Type-1 diabetes, which affects between 5 to 10% (Maahs et al. 2010) of the 450 million people with diabetes worldwide (Cho et al. 2018), the use and expansion of intelligent systems is high. Patients can control their plasma glucose levels several times a day and utilize a subcutaneous and continuous release of insulin with a pump to avoid hypoglycemia. Nowadays, the administration of insulin can be self-regulated by a system that tunes the drug release according to the measurement of physiological signals in real-time. The "artificial pancreas" directly mimics the pancreatic cells to deliver a proper dose of insulin at the

appropriate time in agreement with plasma glucose levels (Yu et al. 2018). The underlying complex algorithm reduces the daily-life burden of type-1 diabetes and significantly improves glucose control (Bekiari et al. 2018) while being safe for the user in unsupervised situations. In another example, patients with acute respiratory failure in intensive care units may safely benefit from automatically adjusted mechanical ventilation to improve synchrony between the patient and the ventilation device (Arnal et al. 2013). Adaptive servo-ventilation is another application of a closed-loop system that can improve sleep fragmentation and sleep efficiency in patients with chronic heart failure having central or obstructive sleep apnea (Hetzenecker 2016).

In neurological disorders, closed-loop systems have also already been used effectively and safely in the treatment of epilepsy to suppress discharges via neuro-stimulation of the targeted cerebral regions via an implanted device (Osorio et al. 2001; Anderson et al. 2008; Vassileva et al. 2018). Closed-loop systems are innovative tools for neuro-prosthetics or rehabilitation. They have tremendous potential to refine actions of a controllable robotic limb (Patil and Turner 2008; Rijnbeek, Eleveld, and Olthuis 2018), and to improve recovery of motor function due to paralysis or stroke (Levi et al. 2018). Neuro-modulation based on DBS for Parkinson's disease has also shown evidence of clinical benefits. Adaptive DBS (aDBS) has been proposed to better fit the needs of stimulation, limit its adverse effects, and preserve the battery life of the neuro-stimulator. This technique intends to deliver stimulation only if necessary, and with specific parameters, conforming to the monitoring of a selected parameter of interest. Several approaches regarding the stimulation features have been studied depending on PD phenotypes (*e.g.*, amplitude-responsive or phase-responsive DBS), and various input signals have been used to optimize adaptive stimulation according to the symptomatology. The available parameters of interest for aDBS could be electrophysiological recordings such as the local field potentials of Basal Ganglia (signal reflecting the activity of a group of neurons, which

can be measured by the implanted electrodes of a DBS), cortical recordings with electrocorticography, surface electromyography, or markers of symptoms objectively quantified by wearables sensors, or subjectively reported by eHealth or mHealth applications (Habets et al. 2018). The recording of neurochemical dynamics might be another solution but it has not yet been explored in humans (Kuo, White-Dzuro, and Ko 2018). Nonetheless, the smart neuro-modulation of DBS in real-time is personalized to the patient and has shown efficacy, efficiency, and superiority compared to conventional DBS (Little et al. 2013). Typically, hand tremor can be reduced with a closed-loop DBS as a function of an inertial monitoring of tremor severity (Herron et al. 2017), or with controlled stimulation of both STN and GPi via electromyography of the hand muscles (Gheisarnejad et al. 2020). Moreover, some brain rhythms could be associated with specific PD symptoms (Mitchell and Starr 2020), enabling the elaboration of the closed-loop system into a unique device that would both monitor and act. Beta oscillations with abnormal patterns and high amplitude have been described as the first marker useful to control bradykinesia with aDBS (Weinberger, Hutchison, and Dostrovsky 2009). Also, high gamma oscillatory activities have been identified as dyskinesia, indicating a need to decrease stimulation voltage (Swann et al. 2018). Online neuronal activities recording and analysis are intimately tied to very powerful technology, and we still are in the early stages of development, even if aDBS is foreseen to be superior to the current modulation of DBS (Rosin et al. 2011). Some logical concerns may appear when using connected systems, mainly about communication security of its different elements to guarantee protected device accessibility and data content. This is a reason why a multidisciplinary effort and additional studies are needed in the emergence of aDBS (Habets et al. 2018; Kuo, White-Dzuro, and Ko 2018; Meidahl et al. 2017; Beuter, Lefaucheur, and Modolo 2014). Current limitations in clinical trials are still an obstacle to proving complete efficacy and efficiency of aDBS (Bouthour et al. 2019). Further validation of both the operative and the controlling units of this

closed-loop is needed. Indeed, aDBS can be based on various variables, which should be set, and then on different sensors, to assure that accuracy is clearly established. Also, the link between the measure and the reaction in DBS requires additional proof before any implantable medical device is commercially available for long-term PD treatment.

Another example of closed-loop systems applied for PD uses cueing. It has already been widely shown that auditory (Cochen De Cock et al. 2018; A Nieuwboer et al. 2007; Thaut et al. 2019; Bella et al. 2018; Mirelman et al. 2011; Ginis et al. 2017), visual (Donovan et al. 2011; Barthel 2018) and tactile cueing can improve the motor symptoms of PD patients, especially gait fluidity, FoG and falls. In open-loop systems, patients generally adapt their behavior after hearing or seeing a cue (*e.g.*, the beat of a metronome or a laser line on the ground). Concurrently, in closed-loop systems, the cueing parameters can be adapted to real-time behavior, for instance, offering real-time audio feedback dependent on the gait phase (Casamassima et al. 2014). As an illustration, trials with tactile closed-loop cueing showed improvements in gait (Stuart and Mancini 2019), and turning smoothness (Mancini et al. 2018) without compromising the realization of a parallel cognitive task. The REMPARK project intended to provide auditory cueing from the monitoring of a BWS, and the tailoring of treatment by neurologists in the long-term (Albert Sama et al. 2014). The REMPARK system also took into consideration nonmotor symptoms as auto-questionnaires were available via smartphones. However, to the best of our knowledge, the described system has not yet been realized.

Finally, a closed-loop system was the aim of a proof-of-concept study in the adaptive delivery of apomorphine in patients with advanced PD (A. Rodríguez-Molinero et al. 2015). Rodríguez-Molinero et al. studied the impact of variations in apomorphine infusion rates on motor state from an assessment of symptoms. While their sample size was low, they showed feasibility with a first trial of remote and real-time control of apomorphine doses adaptations. During this

study, adjustments of the pump parameters were performed manually after a call every two hours from the physician to the patient who reported the changes in ON/OFF motor state. However, this study involved the exploration of intelligent dosing for CSAI therapy, and extended closed-loop treatment systems in PD aside from DBS. Pumps may also be a good candidate for adaptive control of therapy according to the objective monitoring of symptoms, which is feasible with BWS.

Closed-loop systems can be implemented in a variety of ways, and they are usually a sign of improvements in symptom management. To date, they depend on digital health technologies capabilities. The adoption of closed-loop systems in care has to undergo the acceptance of health professionals, whom interest and involvement should reflect a need to improve clinical practices, and of patients, who need to accept living with connected devices, with limited intrusion into their life and assured health data security. The choice of the parameter of interest to be recorded and which will be the basis of a treatment action needs to be further examined. The process for an action decision also requires robust algorithms, which should be evaluated carefully to ensure confidence in a system that does not rely on human actions.

1.3 System composition of a hypothetical closed-loop system applied to PD management

Currently, the implementation of aDBS is not complete, however, this area of research is already well considered. Meanwhile, adaptive delivery of apomorphine from BWS monitoring is still a novel area of research. Therefore, in this work, we considered a hypothetical closed-loop system for PD management that involves CSAI and BWS to better manage motor symptoms from objective monitoring. Numerous development projects have favored the expansion of advanced technology that could be the basis of such an automated system. The

use of BWS is emerging, both for research practice and for standard clinical follow-up, and CSAI can now be applied to various refined pump devices. Still, there is no concrete production of a system related to the automatic delivery of CSAI in line with the monitoring of PD symptoms, and no evidence has demonstrated how to organize or manage this function. However, the smart delivery of apomorphine from objective measurement could lead to improved clinical PD management and available technology is a real opportunity to move forward more personalized medicine (Espay et al. 2016). Each of these closed-loop components will be further detailed in the following sections (Figure 6).

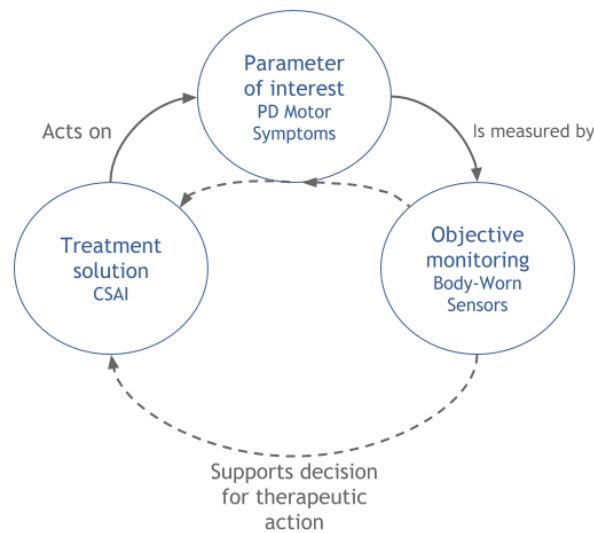


Figure 6: Scheme of the adaptive CSAI based on the BWS monitoring of motor symptoms in line with a closed-loop system. Dashed lines are links uncovered by the literature that we studied in this project.

1.3.1 Parameter-of-interest: motor symptoms

The hallmarks of Parkinson’s disease are motor signs of the disease, namely resting tremor, akinesia, rigidity, and postural instability (Gelb, Oliver, and Gilman 1999). We previously went through a brief description of each of the hallmark, and through the various limits inherent in their clinical assessment by specialist observation during out- or inpatient visits, with scales or the patient’s diary, and by interpretation of the patient’s interview. There are known biases in

the evaluation of those symptoms by experts, and in their perception by patients. Additionally, both subjective and semi-objective quantifications of motor symptoms may lack accuracy. But we also explored the field of objective monitoring, which may fill gaps in the current available solutions in motor symptom assessment. The typical signs of PD can be measured and quantified by BWS in real-life situations at the patient's home to provide a continuous estimation of motor symptoms to clinicians. However, one question needs to be broached: are patients and PD health professionals ready to use such technology? This question will be the interest of our second study.

1.3.2 Therapeutic management with CSAI

Generally, conventional treatments with oral and transdermal medications are proposed for the first years of the disease. Subsequently, after the manifestation of PD complications with fluctuations and dyskinesia, the use of DAT is suggested (Olanow, Calabresi, and Obeso 2020). Long-term support is usually needed for patients with DAT, thus involving caregivers and family more than during the first years of PD. Collaboration with various professionals for health and paramedical care, specialty centers and associations may also help the patient live with this type of interventional therapy after its initiation (Krüger et al. 2016). In general, CSAI is set up during a first long phase during a 1 or 2-week stay at the hospital, and a protocol of inpatient visits of several days may be pre-planned in the long-term. The initiation of CSAI may also be performed in ambulatory care settings, where healthcare providers play a major role. They also are essential in the long-term management of CSAI. Particularly, specialist PD nurses are very important in the day-to-day care of patient pumps at home (Bhidayasiri et al. 2015). Indeed, CSAI therapy entails daily manipulation of the pump for installation and removal or infusion site modification, which is performed by the patient if autonomous or by a nurse, and frequent resupplying of consumables. The follow-up of patients with CSAI depend

on care centers (Hache et al. 2020), and as yet, there are no clear guidelines to validate this process.

No randomized clinical trials have not yet been published to compare the three DAT options, however, a comparative study in real-life settings recently provided cues in the selection of each option in accordance with the objectives of improving specific patient profiles (Dafsari et al. 2019). Motor and non-motor disorders are improved by all three DAT options, but CSAI shows a greater advantage in the improvement of QoL. The impact of CSAI on QoL assessed by PDQ-39 was significantly favorable, overcoming plausible occurrences of adverse events (Drapier et al. 2016). Several studies have shown the efficacy of CSAI in improvement of motor complications:

- time in OFF state is reduced (A. J. Hughes et al. 1993; Colzi, Turner, and Lees 1998; Pietz, Hagell, and Odin 1998; Di Rosa et al. 2003; García Ruiz et al. 2008; Katzenschlager et al. 2005; Antonini and Tolosa 2009; Sesar et al. 2017);
- dyskinesia were reduced in severity in frequency and duration (García Ruiz et al. 2008; Colzi, Turner, and Lees 1998; Manson, Turner, and Lees 2002; Katzenschlager et al. 2005), even though the improvement on dyskinesia can be balanced due to the pursuit of pulsatile intake of levodopa (Antonini and Tolosa 2009; Pietz, Hagell, and Odin 1998; A. J. Hughes et al. 1993);
- time in ON without troublesome dyskinesia was increased after six months (Katzenschlager et al. 2018).

CSAI therapy has also shown beneficial effects on NMS (Pablo Martinez-Martin et al. 2011; Todorova and Ray Chaudhuri 2013; Pablo Martinez-Martin et al. 2015; Auffret et al. 2017). Oral antiparkinsonian drugs are often reduced after initiation of CSAI. For example, the decrease in oral levodopa was significant in several studies:

- at three months, between the apomorphine group and the placebo group of the first randomized controlled trial (Katzenschlager et al. 2018);
- for the 82 patients of the study by Garcia et al. (with 1,405 +/- 536.7 mg of levodopa equivalent units observed at baseline vs. 800.1 +/- 472.9 mg at the end of the CSAI follow-up (19.93 ± 16.3 months)) (García Ruiz et al. 2008);
- for the 93 patients of the study by Sesar et al. (from 1098 ± 313 to 875 ± 396 mg, with a mean duration of CSAI follow-up of 26.3 months) (Sesar et al. 2017);
- between initiation of CSAI and six months for the 12 patients of the study by Auffret et al. (32% decrease of its oral Levodopa Equivalent Daily Dose (LEDD)) (Auffret et al. 2017);
- for the 81 patients of the population in the study by Rambour et al., between the initiation and the end of follow-up (37.8% decrease of oral LEDD after 28 months in average) (Rambour et al. 2014).

Thus, in addition to being efficient in the reduction of PD symptoms, treatment with CSAI may allow various treatment adaptations considering the entire therapeutic management plan to offer the best of therapies to patients.

Adaptive delivery of apomorphine could be possible thanks to the technology in currently available infusion delivery pumps. Implementation can also adopt communication tools to allow the reception of orders to control the administration of apomorphine. Settings of the infusion pump would then be revised accordingly. To date, several pump devices have been developed and commercialized for the subcutaneous infusion of apomorphine; for example, the following products: Crono Par® (Cané, Italia (“Crono Par Pump, Cané” n.d.)), SoConnect® (FDE, France (“SoConnect, FDE” n.d.)), or D-Mine® (Ever Pharma, Austria (“D-Mine, EVER Pharma” n.d.)) (Figure 7).



Figure 7: Examples of infusion pump for apomorphine continuous delivery in PD

Some of these systems already utilize Bluetooth, which currently can be used to collect data from the delivery parameters and could further receive inputs from a closed-loop algorithm. Thus, for the creation of the closed-loop algorithm, a first technical challenge will be to update pump device functionalities. Another challenge is related to the definition of correspondence between the measure of a symptom and the CSAI parameter.

1.3.3 Body-Worn Sensors (BWS)

As previously mentioned, objective monitoring of motor symptoms with BWS may be a significant opportunity for overcoming the limitations of conventional assessments (Warmerdam et al. 2020). BWS can support clinical decision making with high-resolution continuous monitoring of PD symptoms (Erb et al. 2020; Stamford, Schmidt, and Friedl 2015). Even if challenges still remain in the adoption of BWS in clinical practice, they represent an opportunity for closed-loop systems (Espay et al. 2016). Here, we will focus on the objective and continuous monitoring of PD motor symptoms with validated BWS, and especially, we will detail three commercially-available systems that have been certified as medical devices for PD with FDA approval and CE certification.

An increasing number of algorithms and BWS have been developed for PD feature monitoring, both for laboratory exploration and for long-term at home monitoring (Dorsey, Glidden, et al. 2018; Sprager and Juric 2015). The algorithm, type of sensor and its positioning on the body

can differ depending on the monitoring objectives (Pacini Panebianco et al. 2018). The maturity of detection capacities in the different domains of PD symptoms might also differ (Hobert et al. 2014), and this is why specific validated systems may be recommended for the assessment of particular PD features (Godinho et al. 2016). In the research setting, investigations focus on the development of new algorithms and their improvement to better detect the feature of interest (S. Patel et al. 2009), or on the analysis of the best sensor position on the body (Raykov et al. 2020; D. W. Kim et al. 2019; Tietsch et al. 2020; Hubble et al. 2015). In clinical trials, BWS are exploited to improve knowledge about symptoms and characterize them during scripted protocols of physical actions (Greene et al. 2012; 2018). For example, the Ambulatory Parkinson's Disease Monitoring system (APDM®, Inc. Portland, OR, USA) is composed of a sensor (tri-dimensional accelerometer and a tri-dimensional gyroscope) that captures motion during specific exercises realized by the monitored patient. The APDM® technology has been used in numerous trials in motion analysis for more than ten years and was proven reliable in terms of the outcome measures (Ginis et al. 2017; Bertoli et al. 2019; Bonora et al. 2017; di Biase et al. 2018; Mirelman et al. 2016; Ramsperger et al. 2016; Dewey et al. 2014). Gait parameters in PD were especially studied with different types of sensors and worn in various positions, such as the ankle, on shoes, or the shank (Iluz et al. 2014; Schlachetzki et al. 2017; Salarian et al. 2004; Mariani et al. 2013; Zampieri et al. 2010). The system could also extend monitoring to several other disease parameters as done in the SENSE-PARK approach, which utilizes four BWS and several connected devices (Ferreira, Godinho, et al. 2015; Ferreira, Santos, et al. 2015; Serrano et al. 2015), the PERFORM system, which converges the assessment of dyskinesia (Tsipouras et al. 2010), tremor (Rigas et al. 2012), bradykinesia (Pastorino et al. 2011) and gait parameters (Cancela et al. 2011; Cancela, Pastorino, Arredondo, et al. 2014) with five sensors and a connected platform (Pastorino et al. 2013; Cancela, Pastorino, Tzallas, et al. 2014), or the three systems that we selected for this work.

The three systems examined in this work are: PKG® (Global Kinetics Corporation, Melbourne, Australia), Kinesia 360™ (GreatLakes NeuroTechnologies, Cleveland, Ohio, USA), and STAT-ON® (Sense4Care, Barcelona, Spain). These are intended for use in clinical practice as the devices are presented as easy-to-use systems (with one or two sensors) acceptable for patients without medical supervision, and the presentation of result may permit a clear and relatively quick interpretation for applications to actions for PD patients.



Figure 8: PKG Watch®

Worn on the wrist of the PD patient's most affected side of the body

The PKG® system automatically quantifies bradykinesia, dyskinesia, and tremor. The PKG Watch® (triaxial accelerometer at a 50 Hz sampling rate) is in the form of a smartwatch that is worn on the most affected side of the body (Figure 8). After a custom configuration, the PKG Watch® is worn continuously over a 6-day period at the patient's home. The collected data is transferred at the end of the monitoring period to an online platform and processed by a proprietary algorithm to generate a graphical report that displays the evolution of the patient's PD motor symptoms. The results report presents daytime (5 A.M. to 10 P.M.) evolution of bradykinesia (BKS) and dyskinesia (DKS) scores in a main smoothed graph. BKS and DKS are produced every two minutes and can be observed in relation to the scores of subjects without PD in 4 grades of severity (I, II, III and IV). PKG® results are presented in a report that allows

the identification of fluctuations in relation to medication intakes. Other results are presented for tremor occurrence, time of immobility, and time during which the watch was not worn. A summary of results displays quantified scores for bradykinesia and dyskinesia evaluation compared with subjects without PD. A global score for fluctuation is also provided (FDS), as well as the percent of time spent with tremor (PTT), and time immobile (PTI). Finally, the PKG® BKS and DKS of each 2-minute period are presented per day for a micro-visualization of the monitoring results.

The PKG® algorithm has been validated against gold-standard PD assessment methods: evaluation from specialists (Farzanehfar et al. 2018; Johansson et al. 2018), video recording (Griffiths et al. 2012), patient diaries (M. K. Horne, McGregor, and Bergquist 2015), and clinical rating scales such as UPDRS part III (without the tremor item) which evaluates the motor state, and the modified AIMS that assesses motor complications (Braybrook et al. 2016). The PKG® system has been used to study nighttime parameters (M. Horne, Kotschet, and McGregor 2016; Kotschet et al. 2014; McGregor et al. 2018; L. Klingelhoef et al. 2016) and impulse control disorders (Evans et al. 2014). An exploratory study also investigated the potential of BWS to gather information on NMS when monitoring motor symptoms. Associations were made between PKG® scores and different domains of the NMSS, and especially gastrointestinal problems (van Wamelen et al. 2019). There are also emerging applications that modify common care with PKG® in clinical trials. Clinical teams have used PKG® as a supportive tool for therapeutic management (Farzanehfar et al. 2018; Johansson et al. 2018; Lisa Klingelhoef et al. 2016; Santiago et al. 2019; Khodakarami, Farzanehfar, and Horne 2019; Khodakarami et al. 2019), or to improve dialogue between patients and clinicians (Nahab, Abu-Hussain, and Moreno 2019). A blinded controlled trial recently showed that the therapeutic management of patients who needed a medication change was improved with the assistance of PKG® (Woodrow 2020). Moreover, PD experts with long PKG® experience

suggested the identification of target ranges for more effective control of therapy according to the patient's PKG® scores (Farzanehfar and Horne 2017) and others commented on the utility of PKG® for optimizing decisions on antiparkinsonian treatment (Pahwa et al. 2018). An experimentation of PKG® in a telemedicine-like model of care suggested that the use of PKG® can lead to an improvement in the quality of healthcare (Dröschel et al. 2017).



Figure 9: Kinesia 360™ sensors

Worn on the ankle and the wrist of the PD patient's most affected side of the body

Kinesia 360™ monitors tremor, dyskinesia, slowness of movement, and activities and gait parameters. Kinesia 360™ comes in the form of a set of two sensors (triaxial accelerometer and gyroscope at a 32 Hz sampling rate) integrated into two bracelets that are worn on the wrist and the ankle of the most affected side of the body (Figure 9). The system also utilizes a smartphone with an app to transfer the monitored data. After configuring the system for a patient's assessment, the duration of monitoring can vary according to the objectives. Patients have to start and stop the monitoring every day with the application, and every night also need to place the two sensors on a dock station for charging and internet transfer of the data to the web platform. Results are made available each day on the web platform for evaluation by clinicians or researchers. The proprietary algorithm displays daily results as quantitative scores every two minutes. The monitored features of PD are tremor, dyskinesia, slowness of movement, and the number of steps. A quantified summary of the data also shows the total and

percent times with tremor, dyskinesia, and slowness in five grades of severity (0 to 4), and mobility information (resting time, active time apart when walking, walking time, percentage of arm swing during gait). Information can also be collected from the smartphone's app regarding medication intakes and a diary-like questionnaire of symptoms, but this requires the intervention of the patient.

Technical validation of Kinesia 360™ has been staged according to deployment in terms of the algorithm's capacities. The algorithm for automated assessment of tremor has been correlated to the tremor item of the UPDRS with movements that were scripted and performed in clinics (Giuffrida et al. 2009). The detection of tremor was extended to activities of daily living and resulted in the correct classification of tremor types (Heldman, Jankovic, et al. 2011). It should be noted that for these studies, the sensor was worn on the finger and not the hand, as for Kinesia 360™. According to comparisons with evaluations of videos by specialists and UPDRS scores, upper-body bradykinesia detection by the finger-worn sensor was accurate during scripted movements (Heldman, Giuffrida, et al. 2011), as well as for lower-body bradykinesia with heel-mounted sensors (Heldman et al. 2012). Dyskinesia assessment with an arm-worn sensor was also highly correlated with clinical scores for dyskinesia evaluation (Mera, Burack, and Giuffrida 2013; 2012). Moreover, the algorithm successfully quantified motor symptoms such as tremor, dyskinesia or bradykinesia in several studies that explored these features in response to treatment actions (Mera et al. 2011; Espay et al. 2011; Heldman et al. 2014; Mera et al. 2013; Tamás et al. 2016; Akbar et al. 2016). A complete home-setting was tested and validated for continuous monitoring of tremor (Pulliam, Eichenseer, et al. 2014), bradykinesia during specific tasks (Mera et al. 2012), and dyskinesia during activities of daily living (Pulliam, Burack, et al. 2014). Moreover, the system has been used in various situations for application of the algorithm capacities to measure PD symptoms (Ridgel et al. 2011; 2012), and to help in telemedicine PD management (Heldman et al. 2017).

Kinesia 360™ (Figure 9) was used to supplement standard care in adjustments of antiparkinsonian treatment (Isaacson et al. 2019; Heldman, Giuffrida, and Cubo 2016), and to detect fluctuations between ON and OFF states (Hssayeni et al. 2019; Pulliam et al. 2018). This system was involved in the feasibility study of aDBS. The monitoring of PD symptoms with Kinesia 360™ was performed during DBS settings using standard practices, and the collected data was used to develop algorithms for automation of DBS parameters configuration (Pulliam et al. 2015). A pilot study showed the potential efficacy of these algorithms because they could select DBS parameters that significantly improved symptoms in seven patients undergoing DBS parameters programming (Heldman et al. 2016). Those results were preliminary and they still need to be extended by further experiments with more close-to-real-life settings.



Figure 10: STAT-ON®

Worn on the left side of the waist inside a dedicated belt

STAT-ON® assesses ON and OFF states, bradykinesia, dyskinesia, FoG, gait parameters (number of steps, stride speed, cadence, walking time, and step length), number of falls, posture, and energy expenditure. The device (microcontroller and triaxial accelerometer at a 40 Hz sampling rate) is worn in a belt at the waist (Figure 10). After the monitoring configuration, the device is worn by the patient during the daytime and at least for three days, which lets the algorithm auto calibrate to the patient's mobility. Movement analysis is computed

in real-time and a dedicated application installed on a smartphone or tablet can receive the analyzed data to display the results of monitoring anytime. Results of monitoring are presented with quantified summarized values and graphs, displayed for daily and weekly periods.

Technical validation of the algorithm has been performed against synchronized video, patient's diaries and clinical scales, either in laboratory conditions for the first studies with patients, and then in real-life settings at the patient's home for continuous monitoring of PD motor symptoms. Several studies detail the algorithm quantification of gait parameters and description of PD symptoms (Sayeed et al. 2013b; 2013a; Alejandro Rodríguez-Molinero et al. 2015). Bradykinesia is characterized with STAT-ON® by an evaluation of gait parameters, and especially gait fluidity (Pérez-López, Samà, Rodríguez-Martín, Català, and Cebes 2016). STAT-ON® measures bradykinesia with more than 90% accuracy, 88% sensitivity and 81% specificity (Sama et al. 2017). Dyskinesia patterns, especially choreic kinesia that comprise involuntary movements of the trunk and that can be described with a frequency analysis, are assessed with 93% and 95% sensitivity and specificity, respectively (Pérez-López, Samà, Rodríguez-Martín, Moreno-Aróstegui, et al. 2016). To estimate the validity of this assessment, researchers performed a correlation study between clinician judgment with a dyskinesia scale (UDysRS) and the monitoring results (Rodríguez-Molinero et al. 2019). Together with the stride characterization, detection of dyskinesia allowed the evaluation of ON and OFF states (Sama et al. 2012). The assessment of the ON and OFF states by STAT-ON® has been validated with 92% sensitivity and 94% specificity (Pérez-López, Samà, Rodríguez-Martín, Català, Cabestany, et al. 2016; Bayés et al. 2018). STAT-ON® can thus monitor motor fluctuations in the long-term and in real-life conditions at the patient's home (Pérez-López, Samà, Rodríguez-Martín, Català, Cabestany, et al. 2016; Pérez-López et al. 2015). Similarly, the monitoring of FoG shows more than 90% accuracy, with 85% sensitivity and specificity (Rodríguez-Martín et al. 2017; Ahlrichs et al. 2016). The process of validation involved video-based assessment

during ADL performed at home and entailed a personalization of the algorithm to the patient being monitored (Takač et al. 2012; 2013; Camps et al. 2018). Posture also plays a major role in the identification of PD motor symptoms by STAT-ON®. Detecting change in position, such as sit-to-stand, lying or bending down, *etc.*, helps to catch falls in unsupervised behaviors (Rodríguez-Martín, Samá, et al. 2013; Rodríguez-Martín, Pérez-López, et al. 2013).

Until now, BWS have been mainly used for research purposes, and much is still left to be understood about the use of data collected from objective monitoring. Surely, they are not the same as usual information gathered from clinical scales and the physician evaluation (Kubota, Chen, and Little 2016), but specialists in the field of PD can expect much from BWS monitoring to improve symptoms management by better tailoring treatment, which will increase patient QoL (Per Odin et al. 2018; Monje et al. 2019). In addition, intensive research is being performed to constantly improve detection algorithms of BWS and to personalize objective assessment of patient symptoms, which is increasing knowledge about PD motor symptoms. BWS are close to being operational in a closed-loop system, as, for instance, communication modules are often already integrated to collect monitored data (Rodríguez-Martín, Pérez-López, et al. 2013; Ahlrichs et al. 2013).

1.3.4 Decisions for action

In PD, the current organization of care resembles an open-loop system, which actions on treatment are a function of parameters-of-interest evaluations along the continuum of the disease. Decisions on therapy are in line with the symptoms evaluated with current available tools, and they may apply to either individual doses, the number of intakes per day, or the duration, periods, delivered doses and stimulation amplitude and frequency. In a closed-loop system for adaptive delivery of apomorphine, the treatment features that could be regulated by the algorithm are the apomorphine dose and the duration and periods of delivery. In this system,

consequences of treatment actions from monitoring would directly be evaluated by the built-in BWS, which may be more suitable than the current methods of a second inpatient visit, phone call or email.

However, for now, the correspondence between the motor symptom measure by BWS and the actions on treatment performed by neurologists is still at the stage of exploration. There are no exact guidelines regarding adequate therapeutic decisions that match the BWS results. The definition of coherent actions on CSAI from BWS monitoring of the parameters-of-interest is necessary to build an algorithm for a PD closed-loop system, with an aim of improving the impact of treatment on PD symptoms.

1.4 Objectives of the thesis work

Towards the aim of creating an intelligent system to address PD, we went through the possibility of connecting various components together. In order to study each link, three main studies were initiated that complement the existing literature.

First, we aimed to determine if the action on CSAI could be modeled or deduced from a parameter of interest. Such information could be used to feed algorithms that would link BWS monitoring in the follow-up of PD and actions on treatment. Second, we wondered if patients and health professionals would accept BWS monitoring as part of the standard follow-up of PD symptoms. Indeed, whatever the technology-readiness and reliability of BWS, such technology must correspond to the demands of clinicians and possibilities for the daily life use by potential users before being part of the management plan as an individual tool, and then a major actor of the closed-loop. Last, we studied the way treatments may be adjusted from the results of BWS monitoring in order to understand how it can become an accurate routine procedure in PD patient follow-up, and a potential decision process for treatment action in the loop.

2. Therapeutic decisions and PD symptoms: unbalanced interactions

First, we focused on the link between the treatment solution and the parameter-of-interest of a closed-loop system. We studied the impacts of CSAI on PD symptoms, and conversely, we investigated the role symptoms may have on decisions about CSAI, which is less investigated in the literature.

Indeed, in patients with CSAI, an adequate balance with conventional treatment has to be evaluated for several weeks to obtain the best results. Finding this balance between therapies is delicate, and, to date, there are no specific rules that have been shown to accurately identify the correct adjustments to be performed. The study of these coexisting adjustments of conventional and CSAI therapies according to patient profiles and PD features may help highlight a parameter-of-interest for BWS monitoring and define the correspondence between its measure and the decision for CSAI actions. Also, the information on the impacts of CSAI on the parameters-of-interest may also help tune the algorithm for adaptive delivery of apomorphine according to PD symptoms.

2.1 Long-term effect of apomorphine infusion in advanced Parkinson's disease: a real-life study [Submitted]

The study manuscript is available in Supplementary Material I (Meira et al. 2020).

ABSTRACT

Long-term effects of continuous subcutaneous apomorphine infusion (CSAI) on Health-related quality of life (HRQoL) and predictors of CSAI discontinuation are poorly known. We evaluated consecutive advanced Parkinson's disease patients over 24 months after CSAI initiation, using the 39-item Parkinson's disease Questionnaire (PDQ-39) as the primary endpoint. We determined predictors of CSAI discontinuation and HRQoL improvement using multiple regression analysis. Among the 110 subjects evaluated over a two-year period, 35% discontinued CSAI. In those who continued treatment, HRQoL remained stable with a sustained reduction in motor fluctuations.

The effect on dyskinesias was mild and transient. PDQ-39 was the only baseline predictor of HRQoL improvement after two years of treatment. The presence of dyskinesias, poorer psychological status, shorter disease duration, male sex and worse OFF-state were predictors of discontinuation. Best candidates for CSAI are patients: (i) with a poor baseline HRQoL, (ii) who have marked motor fluctuations (iii) in whom dyskinesia are not the main complaint.

This study completes the literature and shows the beneficial effects of CSAI on PD symptoms. As predictors of CSAI discontinuation were revealed, they may also be warnings for potential PD patient candidates of the hypothetical closed-loop system.

2.2 How treatment is adapted in Parkinson's patients under apomorphine: a two-year retrospective study [Submitted] (Virbel-Fleischman, Houot, et al. 2020)

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Word count of Paper: 3691

Running title: Therapies changes with Apomorphine pump

Keyword: Parkinson's disease, Apomorphine, Infusion initiation, Treatment modifications, Therapy strategies

Financial Disclosure/Conflict of Interest concerning the research related to the manuscript: DG received research funding from Air Liquide HealthCare

Funding sources of the study: This study received no specific funding.

ABSTRACT

Background: Continuous Subcutaneous Apomorphine Infusion (CSAI) is efficient for improving fluctuations in Parkinson's disease (PD).

Objectives: This study aims to describe the disease features and patient characteristics that may impact conventional and apomorphine Levodopa Equivalent Daily Dose (LEDD) changes during a two-year follow-up of patients with CSAI.

Methods: We conducted a retrospective study among consecutive patients with PD treated with CSAI. Motor and nonmotor symptoms and treatment adjustments were assessed on initiation of CSAI and after 3, 6, 12, and 24 months. Linear regression and mixed models were performed to investigate the proportion of apomorphine LEDD at baseline and its variation together with the modifications of conventional therapy across the follow-up.

Results: At CSAI initiation, the percentage of apomorphine was significantly influenced by the conventional LEDD on admission and apathy ($p < 0.02$). The two-year variations of apomorphine LEDD were influenced by the variation of conventional LEDD, the absolute value

of apomorphine LEDD and by the visit session ($p < 0.02$). The two-year variations of conventional LEDD depended on the variations of apomorphine LEDD and the absolute value of conventional LEDD ($p < 0.02$). There was no effect of disease features nor their variation across the two-year follow-up.

Conclusions: The balance between conventional treatments and CSAI on initiation was influenced by ASBPD II, without effects of other patients' or PD characteristics. The therapy adjustments over two years were the result of the interplay between conventional and apomorphine doses respectively, without effects of the patients' or disease characteristics.

Abbreviations:

apo: apomorphine

apoLEDD: LEDD of apomorphine

ASBPD: Ardouin Scale of Behavior in Parkinson's Disease

ASBPD II: part II of the ASBPD

COMT-I: catechol-o-methyl-transferase inhibitors

conv: conventional

convLEDD: LEDD of conventional treatments

CSAI: Continuous subcutaneous apomorphine infusion

FAB: Frontal Assessment Battery

HRQoL: Health-related quality of life

HY: Hoehn and Yahr scale

LEDD: Levodopa Equivalent Daily Dose

MAO-I: Monoamine Oxidase Type B Inhibitors

MMSE: Mini Mental State Examination

PD: Parkinson's disease

PDQ-39: Parkinson's Disease Questionnaire 39;

SE: Schwab and England Activities of Daily Living Scale

UPDRS: Unified Parkinson's Disease Rating Scale

UPDRS I: part I of the UPDRS

UPDRS II: part II of the UPDRS

UPDRS III: part III of the UPDRS

UPDRS IV: part IV of the UPDRS

var: variation

varApo: variation of apomorphine LEDD

varConv: variation of conventional treatments LEDD

%apo: proportion of apomorphine

INTRODUCTION

The motor symptoms of Parkinson's disease (PD) are the direct consequence of striatal dopamine depletion. Currently, treatment of PD is based on oral dopaminergic replacement therapy. During the first years of the disease, symptoms are well managed by oral medication but later, as the disease progresses, patients eventually experience fluctuations and dyskinesias. Although various strategies (mainly shortening the interval between L-Dopa doses, acting on L-Dopa pharmacokinetics, and adding the dopamine agonists, COMT-I or MAO-I (1)) have proved effective in reducing motor complications, motor fluctuations may remain out of control in some patients (2–4). At this stage, device-aided treatments can be used to achieve continuous administration and allow for better control of fluctuations and dyskinesia (5). These available advanced therapies include deep brain stimulation, L-Dopa jejunal infusion, and Continuous Subcutaneous Apomorphine Infusion therapy (CSAI). All these treatments have been found to be efficacious in reducing the duration of OFF time periods and time with troublesome dyskinesia (6–8). In line with early uncontrolled open-label studies (9–12), one randomized, placebo-controlled, double-blind, and multicenter trial showed that CSAI was superior to oral therapy in reducing OFF time in PD patients with motor fluctuations (7). Several studies have also suggested that CSAI therapy may help reduce dyskinesias (9,12–14) and improve disease-related quality of life (15). Thus, CSAI is an interesting option for advanced PD patients, but the dose must be carefully set to achieve a

balance between control of PD symptoms and apomorphine-related side effects (dyskinesia, nodules, nausea, orthostatic hypotension, hallucinations, impulse control disorders, and confusion (15,16)). The parameters of the therapy, mainly infusion rates and infusion duration over 24 hours are critical because they directly influence the efficacy and safety of the CSAI treatment, and depend on disease severity and characteristics, and each individual drug tolerance. These parameters are set up during the initiation of the pump and periodically re-evaluated according to the evolution of the symptoms. An adequate balance between conventional Levodopa therapy and CSAI treatment is usually obtained after several weeks or months requiring multiple in- or outpatient visits (7,9–12). To the best of our knowledge, there are no guidelines that may help a clinician decide on specific apomorphine parameters at the starting of CSAI and during follow-up, based on the patient's profile. Through retrospective analysis of a cohort of consecutive PD patients seen in a single tertiary referral movement disorder center, we investigated whether conventional medication and apomorphine doses adaptations from CSAI initiation to 24 months follow-up may be deduced by patients' characteristics. Thus, the main objectives of this study are two-fold: i) to explain the apomorphine Levodopa Equivalent Daily Dose (LEDD) at CSAI initiation, and ii) to describe the evolution of apomorphine and conventional LEDDs according to the patients' profile and concomitant dopaminergic treatments.

METHODS

We conducted a retrospective study among consecutive patients with PD motor complications initiating CSAI therapy over a six-year period at La Pitié-Salpêtrière Hospital (Paris). All patients fulfilled the Movement Disorder Society Clinical Diagnostic Criteria for PD, and CSAI initiation was decided by an expert neurologist of the team after medical evaluation and patient agreement prior to inclusion in the study. A local ethics committee (CPP Île de France 6, Paris) approved this study (observational study of evidence class IV) and the data collection was approved by the national commission for data protection (CNIL). The patients were informed

that their medical information could be used for research purposes after anonymization. The ethics committee did not require written consent.

Treatment procedure

CSAI therapy was initiated in patients during a two-week hospital stay (baseline, M0). There was no pre-specified procedure of dose adaptation for CSAI and conventional treatments. The initial infusion rate of CSAI was usually 0.5 to 1 mg/h over a 12- to 24-hour period, and was gradually increased according to individual tolerance and efficacy. In parallel, the conventional medication could be progressively tapered down. Five-day inpatient follow-up was systematically scheduled after 3, 6, 12, and 24 months (M3, M6, M12, and M24, respectively). During these stays, CSAI parameters and conventional treatments could be further adapted to achieve the best motor state and to minimize side effects. In addition, therapies could be modified according to the patient's needs between hospital stays, either during pre-scheduled or emergency outpatient clinics, or phone calls with the treating neurologist.

Clinical assessment

Demographic data (age, gender, age at disease onset, disease duration) were collected at baseline.

Multidimensional clinical assessment was performed at each inpatient's pre-scheduled visit. To evaluate motor status, we used the Unified Parkinson's Disease Rating Scale (17): the part II (activity of daily living, UPDRS II: range [0, 52]) scored in OFF and ON states, the part III (motor score, UPDRS III: [0, 108]) scored in the ON condition, the part IV (motor fluctuations, UPDRS IV: [0, 23]), the Hoehn and Yahr scale (HY: [0, 5]) in ON and OFF conditions (18,19), and the Schwab and England Activities of Daily Living Scale (SE: [0, 100%]) in ON and OFF conditions (20,21). Non-motor symptoms and cognition were assessed with the UPDRS part I (UPDRS I: [0, 16]), the Mini Mental State Examination score (MMSE: [0, 30]) (22), and the Frontal Assessment Battery (FAB: [0, 18]) (23,24). We decided *a priori* to evaluate changes in mood and behavior related to dopaminergic medication with the Ardouin Scale of Behavior in Parkinson's Disease (ASBPD: [0, 84]) (25) and the part II of the ASBPD (overall functioning in apathetic mode, ASBPD II: [0, 4]). Finally, we used the Parkinson's Disease Questionnaire-39

(PDQ-39: [0, 100]) (26,27) to assess health-related quality of life (HRQoL). Except for the MMSE, the FAB, and the SE assessments, for which the higher the score the better the performance, higher scores of the scales and questionnaires indicated more severe symptoms. Finally, adverse effects were recorded at each visit.

Collection of treatment doses

CSAI and/or conventional (oral and transdermal) treatment doses and schedules were systematically collected for each visit on admission (a) and discharge (d).

Levodopa Equivalent Daily Doses (LEDD) of antiparkinsonian treatments were computed following Tomlinson et al. (28). Apomorphine LEDD (apoLEDD) was equal to the daily infusion delivered by the pump for the prescribed duration and at a determined rate. Conventional LEDD (convLEDD) was the sum of all anti-parkinsonian treatments according to each dose and daily intake. Total LEDD was the sum of apoLEDD and convLEDD.

Statistical analysis

Quantitative data were expressed as median [1st quartile, 3rd quartile] or as percentage.

Apomorphine at baseline

Among the 118 patients of the full cohort, 89 with no missing data at baseline were included in this analysis. In order to study the impact of several parameters (*i.e.* gender, age, PD duration since diagnosis, UPDRS I, UPDRS II ON, UPDRS II OFF, UPDRS III ON, UPDRS IV, HY in ON, HY in OFF, SE in ON, SE in OFF, MMSE, FAB, PDQ-39, ASBPD, ASBPD II, conventional LEDD, percentage of agonists LEDD in total LEDD) on the initiation of CSAI, we performed a linear regression on the percentage of apoLEDD in total LEDD (%apo). %apo was computed as the ratio of apomorphine LEDD and total LEDD. First, we performed simple linear regressions for pre-selection of the variables of interest, with $p < 0.2$ (see Supplementary Table 1). Variables forced in the multiple model were age, gender, PD duration, and conventional LEDD before the initiation of CSAI.

Apomorphine and conventional treatment variations across two years of follow-up

To investigate the concomitant evolution of convLEDD and apoLEDD, two linear mixed models were performed with random intercept for patients. The dependent variables were the

percentage change of convLEDD and of apoLEDD in each adjacent visit (varConv and varApo, respectively). Precisely, $varConv = \frac{convLEDD\ visit\ i - convLEDD\ visit\ i-1}{convLEDD\ visit\ i-1} \times 100$, and $varApo =$

$\frac{apoLEDD\ visit\ i - apoLEDD\ visit\ i-1}{apoLEDD\ visit\ i-1} \times 100$. For both varConv and varApo, the fixed effects were

selected to maximize the patients' number with no missing data in the relevant clinical parameters. Fixed effects were visits, gender, age at baseline, PD duration at baseline and for the following score, the value at the visit, and its percentage change from the previous visit: UPDRS II in ON, UPDRS II in OFF, UPDRS III in ON, HY in OFF, MMSE, FAB, PDQ-39, ASBPD II, and the percentage change of apoLEDD and convLEDD for varConv and the percentage change of convLEDD and apoLEDD for varApo. For these models, we have selected the 114 patients with usable data (*i.e.* with no more than one missing visit except in case of CSAI arrest). When patients discontinued CSAI, their data were included up to the last follow-up visit. Thus, data from patients could be included in the analysis even if the patient were not present at all the visits. All two-way interactions were added in the multiple model independently. The final model includes the significant interactions at $p < 0.05$.

For both linear regressions, type II F-tests were used. Cohen's f^2 were calculated to assess effect sizes. The normality of the residuals as well as heteroscedasticity were checked visually. Cook's distances and hat values were calculated to identify influential data. Analyses were re-run without subjects with Cook's distances higher than $4/n$ (29). The factors' coefficients, standard errors, the Cohen's f^2 , and p-values were extracted from the linear regression and the linear models to present the results.

Statistical analyses were performed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

RESULTS

Treatments evolution over two years

Due to the initiation of CSAI therapy, the apoLEDD increased between M0_a and M0_d, while the convLEDD decreased (Figure 1). On admission for CSAI initiation, total LEDD was 1287

[970, 1520] mg vs. 1426 [1089, 1837] mg on discharge. The total LEDD increased gradually across the two years of follow-up (1663.50 [1177.00, 21188.18] mg on discharge of M24). Also, among the 118 patients initiated with CSAI therapy on discharge of M0, 64 were still included in the study on discharge of M24, and 62 of them maintained this treatment.

Factors associated with the proportion of apomorphine LEDD at CSAI initiation

We first sought to determine which factors could influence the balance between conventional and apomorphine LEDDs at the end of the initiation period. Among 118 consecutive patients, 89 were included in the analysis, 29 patients were excluded because of missing data. Included patients (Table 1) were diagnosed with PD 11 [8.00, 15.00] years before the study. Patients' HY in OFF was 3.00 [2.50, 4.00]), and they were not cognitively impaired (MMSE at 28.00 [25.00, 30.00]). convLEDD on M0_a was 1297.50 mg [973.75, 1490.00]. Excluded and included patients differed on UPDRS I (3.50 [2.00, 5.00] and 2.00 [2.00, 4.00], respectively, $p=0.030$), and FAB (15.00 [12.00, 17.00] and 17.00 [15.00, 18.00], respectively, $p=0.004$) (Supplementary Table 2). No patients were withdrawn due to Cook distances.

Our model revealed that the percentage of apomorphine in the total LEDD on M0_d was influenced by two variables: the convLEDD on M0_a and the ASBPD II (Figure 2). The higher convLEDD on M0_a, the lower %apo after initiation (coefficient: -11.06 ± 4.63 , $f^2=0.070$, $p=0.019$ (the value was divided by 1,000 to make the coefficient readable); Figure 2.A). For the ASBDP part II, higher scores were associated with higher %apo on M0_d (8.50 ± 3.02 , $f^2=0.098$, $p=0.006$; Figure 2.B).

There was no significant effect of gender, age, duration of PD, UPDRS I, UPDRS II in ON, UPDRS II in OFF, UPDRS III in ON, UPDRS IV, HY in ON, HY in OFF, SE in ON, SE in OFF, MMSE, FAB, PDQ-39, the total score of ASBPD, and the proportion of Agonists LEDD on M0_a.

Variation of apomorphine across the two-year follow-up

We then sought to understand which factors could influence the variation of apomorphine dose from visit to visit across follow-up. 113 patients were included in the analysis (one patient was withdrawn after evaluation of the Cook distances and hat values). Included and excluded

patients differed on UPDRS I (2.00 [2.00, 4.00] and 5.00 [3.00, 6.00], respectively, $p=0.025$) and the FAB score (17.00 [14.75, 18.00] and 14.00 [9.00, 16.00], respectively, $p=0.022$).

According to our model, three factors were independently associated with varApo between each visit across the two-year follow-up (Figure 3): inpatient visit ($f^2=0.035$, $p=0.004$; Figure 3.A), varConv (the higher the varConv, the lower the varApo: 0.01 ± 0.04 , $f^2= 0.013$, $p=0.011$; Figure 3.B) and absolute value of apoLEDD (the greatest modifications of apoLEDD were performed for the highest values of apoLEDD: 10.19 ± 2.68 , $f^2=0.046$, $p<0.0001$; Figure 3.C). Finally, the interaction between inpatient visit and varConv had an effect on varApo, meaning varConv influenced varApo differently, depending on the inpatient visit ($f^2= 0.032$, $p=0.009$; Figure 3.D).

There was no significant effect of gender, age, and duration of PD on varApo. Also, neither the absolute values nor the variation of the UPDRS II in ON, UPDRS II in OFF, UPDRS III in ON, HY in OFF, MMSE, FAB, PDQ-39, ASBPD II had a significant effect on varApo (Supplementary Table 3).

Variation of conventional treatments LEDD across the two-year follow-up

We then aimed to identify which factors could influence the variation of conventional doses from visit to visit across the follow-up. 113 patients were included in the analysis (one patient was withdrawn after evaluation of the Cook distances and hat values). Included and excluded patients differed on UPDRS I (2.00 [2.00, 4.00] and 5.00 [3.00, 6.00], respectively, $p=0.025$), SE in OFF (0.60 [0.40, 0.70] and 0.30 [0.20, 0.40], respectively, $p=0.021$), FAB (17.00 [14.75, 18.00] and 14.00 [9.00, 16.00], respectively, $p=0.014$), and the ASBPD II (0.00 [0.00, 1.00] and 1.00 [1.00, 1.50], respectively, $p=0.047$).

According to the model, the changes in convLEDD across the two-year follow-up were associated with two variables (Figure 4). Mirroring the previous results obtained, the higher varApo, the lower varConv (0.09 ± 0.15 , $f^2=0.019$, $p=0.001$; Figure 4.A). varConv was linked to convLEDD, *i.e.* the greatest modifications of convLEDD were performed for the highest values of convLEDD (44.92 ± 7.05 , $f^2=0.092$, $p<0.0001$; Figure 4.B). The interaction between varApo and convLEDD also influenced varConv, meaning that varApo impacted varConv

differently according to the level of convLEDD (-0.38 ± 0.16 , $f^2=0.011$, $p=0.012$; Figure 4.C). The other factors that significantly influenced the varConv were (i) the interaction between the inpatient visit and convLEDD, meaning that the variations of conventional LEDD depended on the level of convLEDD during each specific inpatient visit ($f^2=0.038$, $p=0.003$; Figure 4.D), and (ii) the interaction between the inpatient visit and the PDQ-39 score influenced varConv, *i.e.* varConv changed across inpatient visits, depending on the quality of life ($f^2=0.028$, $p=0.030$; Figure 4.E).

There was no significant effect of inpatient visit, gender, age, or duration of PD. Moreover, neither the absolute values nor the variations of UPDRS II in ON, UPDRS II in OFF, UPDRS III in ON, HY in OFF, MMSE, FAB, PDQ-39, or ASBPD II had a significant effect on the varConv (Supplementary Table 4).

Relationship between the variation of conventional LEDD and the variation of apoLEDD

Finally, as both therapies logically influenced each other (Figure 3.B and Figure 4.A), we tried to better understand this relationship. For both types of treatments, the higher the level of LEDD, the greater the treatments' modifications in proportion to total LEDD (Figure 3.C for varApo and Figure 4.B for varConv). The variations of both therapies were opposite: when the apoLEDD was increased, the convLEDD was decreased (Figures 3.B and 4.A). However, the variations were not equivalent between the two therapies. For instance, the apoLEDD was increased in greater proportions than the conventional LEDD was decreased: an increase of 1 point of varApo corresponded to a decrease of -0.25 ± 0.07 of varConv.

DISCUSSION

In this real-life study, we show that the balance between conventional treatments and CSAI on initiation was influenced only by ASBPD II, without effects of other patients' or PD characteristics. Similarly, the therapy adjustments over two years were mainly the result of the interplay between conventional and apomorphine doses respectively, without effects of the patients' or disease characteristics. In addition, both on initiation and during follow-up, a

decrease of conventional LEDD is associated with a higher increase of apomorphine LEDD, resulting in a tendency towards an increase of total LEDD.

This retrospective and observational study was conducted in routine care conditions, which favor generalization to clinical practice more effectively than randomized controlled trials. To our best knowledge, this is the first study that specifically described the dose trajectory of CSAI and conventional treatments together with the clinical factors that may have influenced this trajectory over 2 years. Another strength of our work is that, apart from cognitive status (no patient had major cognitive decline), our sample is heterogeneous in terms of the severity of motor symptoms or demographics, reflecting a wide range of situations and increasing the relevance of our statistical models. Yet our findings need to be replicated in an independent dataset to tone down the monocentric effect of this study. Assessment did not include patients' diaries, the most effective instrument for capturing fluctuations and dyskinesia, but which is complex to implement in a routine setting. We were not able to include in our model the frequency of severity of adverse events that may play a major role in CSAI doses limitation although they are captured by HRQoL scale, ASBPD and UPDRS I. Another weakness is the number of missing data, due to the study design. We decided not to consider discontinuation of CSAI as a dose adaptation and to focus on how treatment was managed for all the patients still on CSAI. At two years, 53% of the patients in our cohort were still on CSAI, a figure comparable to other studies (7,30,31). This obliged us to consider the treatment adaptation at each visit as independent events, to avoid discarding patients that would have incomplete data over the entire follow-up. However, as our objective was to highlight the factors that influence the balance between apomorphine and conventional treatment and not to assess the efficacy of CSAI, this approach is relevant.

We showed that CSAI initiation was associated with a reduction in conventional LEDD, as expected. The conventional antiparkinsonian drugs were decreased in most studies on apomorphine, whatever the time point between 3 and 28 months after CSAI initiation (7,10,30–32). However, little is known about the natural history of LEDDs' evolution during the entire

course of PD, and particularly at the advanced stage, and about the factors that may influence this evolution.

The longitudinal nature of our study across a two-year period highlights that the shift from conventional treatment to apomorphine is done as early as three months after initiation without any major subsequent change. Also, significant modifications of both therapies resulted in a total LEDD increase of 200 mg over the first three months after CSAI initiation. This is very similar to the figure obtained six months after CSAI instauration by Auffret et al. in a smaller sample (n=12) (32), but higher than expected in a short period of time compared to the usual shift of LEDD observed with conventional treatment. The variation of the total LEDD at three months could not be calculated in the apomorphine arm of the TOLEDO study but it was decreased by around 150 mg in the placebo arm (7). In an open-label randomized control comparing the effect of STN-DBS with the best medical treatment (excluding CSAI) at six months, the total LEDD in the medical treatment arm was decreased by 95 mg (8). The total LEDD increase after three months observed in our study may be explained by the fact that switching to CSAI allows answering unmet needs by using conventional treatment such as the addition of nighttime treatment with apomorphine delivery by night.

One main finding was the relative independence of the balance between apomorphine and conventional LEDDs from patients' or disease characteristics, which may be surprising. Indeed, patients were followed-up by an expert team without pre-specified guidelines, and treatment was adapted only by weighing the benefits and risks of side effects, a ratio that should be linked to patients' and disease characteristics. In the present study, we focused on the balance between apomorphine and conventional treatments. It is probable disease characteristics are already reflected in the total LEDD at inclusion, since it has previously been shown to increase with PD severity (33). Interestingly, the only disease characteristic that influenced the proportion of apomorphine at CSAI onset was apathy. This is in line with previous data suggesting that apomorphine, like other dopaminergic agonists, may improve apathy and mood (32). No effect of patients' or disease characteristics on the conventional versus apomorphine doses ratio was observed later in the two-year follow-up. To the best of

our knowledge, only a few studies have addressed the question of the clinical factors that may determine the trajectory of PD drug doses over a two-year period at the advanced stage. The relative stability of total LEDD in PD patients with disease duration above 6 to 10 years has already been shown (34). A ceiling effect on clinical improvement may be achieved shortly after CSAI initiation and would preclude any significant changes in the apomorphine versus conventional LEDD balance. Additionally, even if widely used, the UPDRS scale may not be the only clinically relevant information to adapt PD therapy in patients with dyskinesia and fluctuations, whose motor state is better captured by diaries (35). Clinicians may adapt treatments with respect to other parameters such as dysautonomia or adverse events that are not directly reflected by the scales we used, apart from the quality of life. Indeed, in our study like in others, HRQoL was shown to influence the adaptations of conventional therapy (36,37). Based on our results on the balance between conventional and apomorphine treatments at CSAI initiation and long-term follow-up, relevant insights for care organization may emerge from this study. First, for a broad category of PD patients the apomorphine/conventional therapy balance may be standardized based mainly on pre-CSAI total LEDD. Second, the schedule of doses should be closely monitored during the first three months, whereas subsequent changes in the long term are marginal (except for the decision to terminate CSAI). Third, objective, continuous, and automated monitoring can be used to assess motor symptoms via wearable devices, for example. Relevant information from those alternative outcome measures might be collected to improve treatment adaptations (38).

AUTHOR'S ROLES

- 1) Research project: A. Conception, B. Organization, C. Execution;
- 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
- 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

CVF: 1A, 1B, 1C, 2A, 2C, 3A, 3B

MH: 1B, 1C, 2A, 2B, 2C, 3B

YR: 1A, 1B, 1C, 2A, 2C, 3A, 3B

SH: 1A, 3B

EC: 1B, 1C, 3B

AS: 1C, 3B;

EB: 1C, 3B

EH: 1C, 3B

PD: 1C, 3B

AM: 1C, 3B

LLM: 1C, 3B

CD: 1C, 3B

FC: 1C, 3B

DB: 1C, 3B

NV: 1C, 3B;

CT: 1C, 3B

LM: 1C, 3B

HL: 1C, 3B

MV: 1C, 3B

JCC: 1C, 3B

BD: 1A, 1B, 1C, 3B

ER: 1A, 1B, 3B

DG: 1A, 1B, 1C, 2A, 2C, 3A, 3B

FINANCIAL DISCLOSURES OF ALL AUTHORS FOR THE PRECEDING 12 MONTHS

MH, EC, AM, CT, AS, EB, PD, LLM, FCD and MV declare no financial disclosure.

CVF received a grant from Association Nationale de la Recherche et de la Technologie (A.N.R.T.) and full-time employment by Air Liquide Healthcare.

YR and SH disclose full-time employment by Air Liquide Healthcare.

EH served on scientific advisory boards for Medtronic and Boston Sci, received honoraria for speeches from Boston Sci, received travel grants from Merz.

CD received research grants from the Federation internationale de l'automobile and travel funding from Merz, Boston Scientific and Medtronic.

DB received travel grants from Boston Scientific and research support grant from Fondation Recherche Médicale.

NV received research support from Fondation Bettencourt-Schueller, Fondation Servier and Fondation pour la Recherche sur l'Alzheimer; travel grant from the Movement Disorders Society, Merz-Pharma and GE Healthcare SAS.

LM received a travel grant from Orkyn (Air Liquide), Abbvie, Elivie, Medtronic.

HL received a travel grant from Orkyn (Air Liquide), Abbvie, Elivie.

JCC served on advisory boards for Air Liquide, Biogen, BrainEver, Denali, EverPharma, Prevail Therapeutic, UCB, and received grants from Sanofi outside of this work.

BD received honoraria from Ipsen Pharma and Elsevier.

ER served on scientific advisory boards for Orkyn, Aguetant, received honoraria for speeches from Orkyn, Aguetant, Everpharma, received research support from Orkyn, Aguetant, Elivie, Everpharma, received travel grant from Vitalair, PEPS development, Aguetant, Orkyn, Elivie, Adelia Medical.

DG received grants from AP-HP (DRC-PHRC) and France Parkinson, served on scientific advisory boards for AbbVie and Zambon; received speech honorarium from Medtronic, Abbvie and Merz; received travel funding from Abbvie and Merz.

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FIGURES

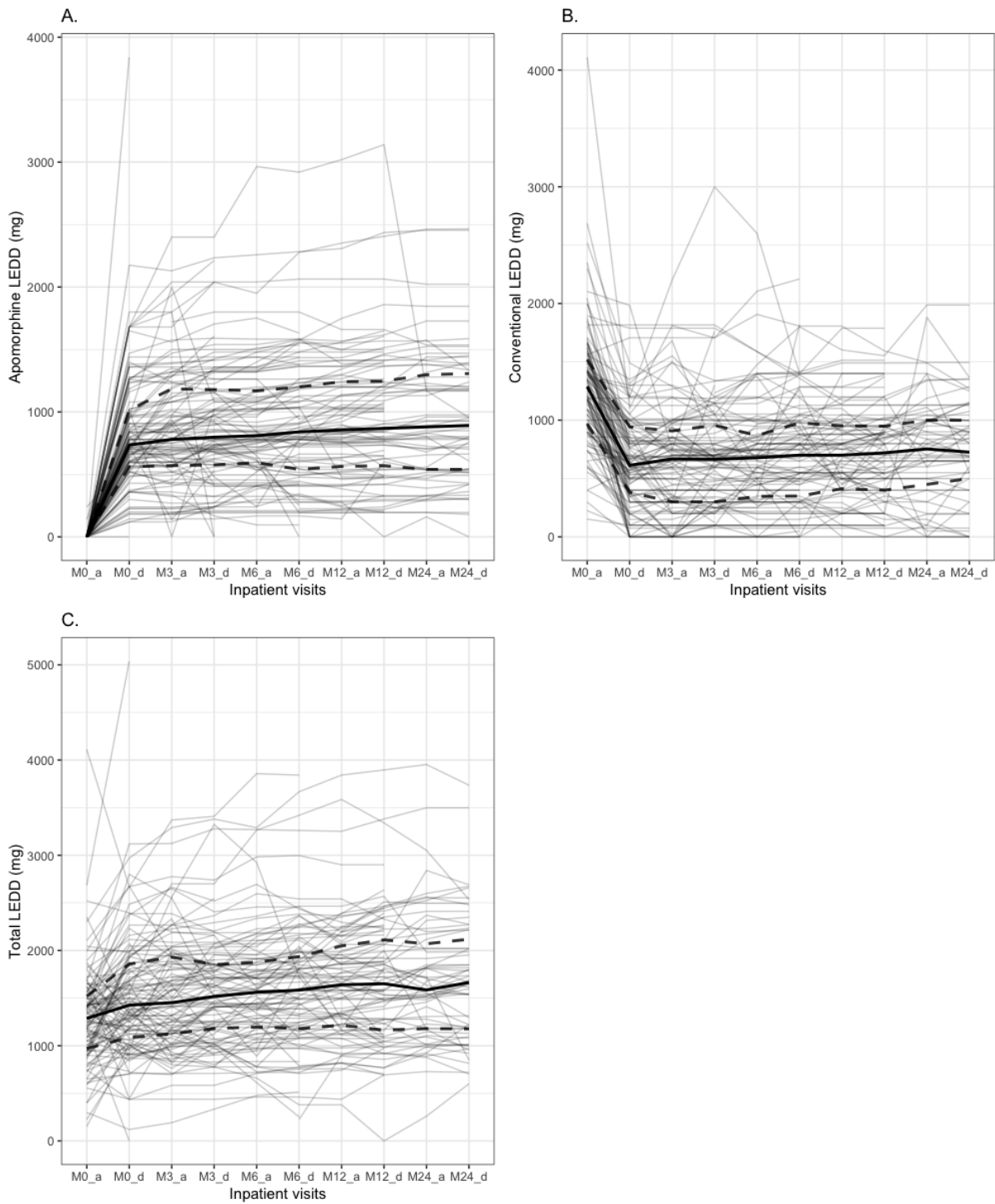


Figure 1: Evolution of the LEDDs from initiation of CSAI and over 2 years

Representation of apomorphine (A), conventional (B) and total (C) LEDDs across the 2-year follow-up. Each patient LEDD for each visit (M0, M3, M6, M12, and M24) at admission (a) and

discharge (d) are represented in black thin lines. Medians, and first and third quartiles are represented in bold lines and dashed lines, respectively.

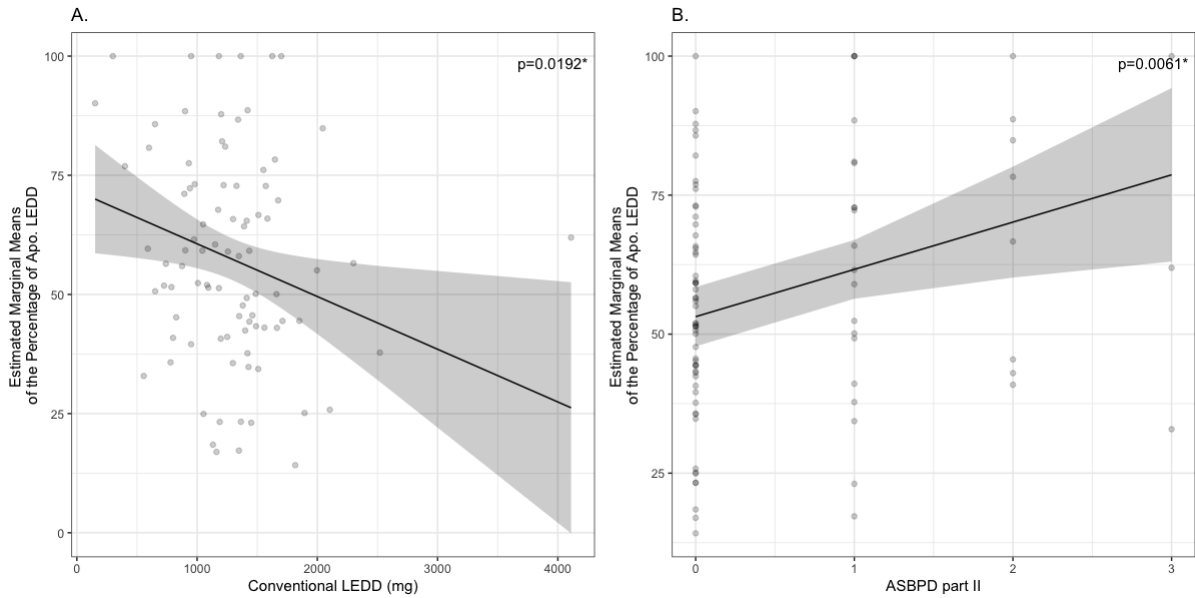


Figure 2: Apomorphine LEDD at baseline

Estimated marginal means of %apo at baseline using a linear regression as a function of conventional LEDD (A) and ASBPD II (B). The black full-lines represent the regression with the confidence intervals in grey. Each dot represents the values of convLEDD (A) and ASBPD II (B) for a single patient and visit.

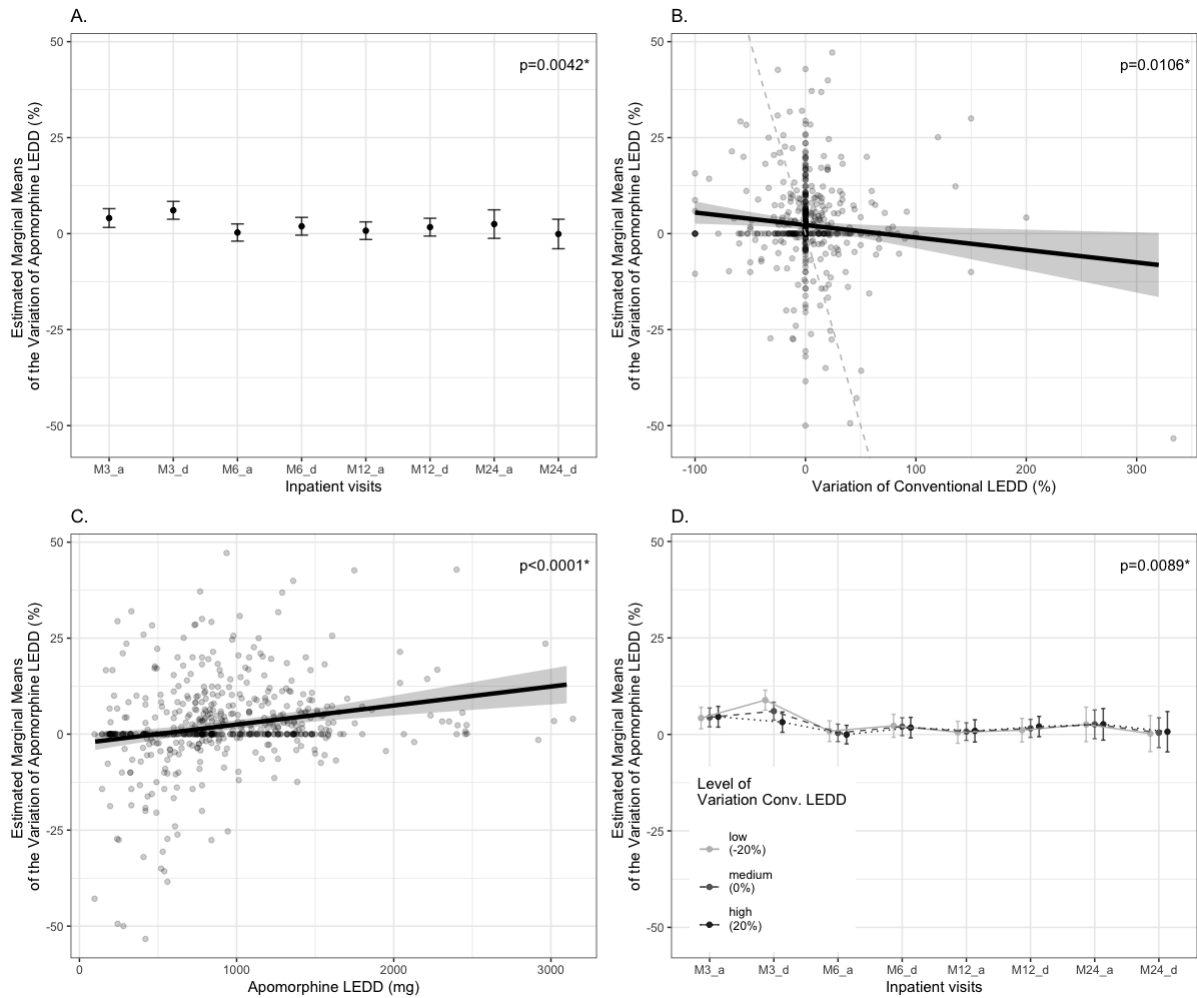


Figure 3: Variation of apomorphine LEDD during 2 years follow-up

Estimated marginal means of varApo using the linear mixed model expressed as a function of the inpatient visit (A), varConv (B), apoLEDD (C), and the interaction between the inpatient visit and the level of varConv (D)

In (B) and (C), each dot represents varApo for a single patient and visit, the black full-line represents the regression with the confidence intervals in grey. In (B), the dashed line represents the theoretical equivalence of varConv vs varApo. In (D), the patients were divided in three groups to illustrate the interaction according to varConv.

a: admission for the inpatient visit start

d: discharge for the end of inpatient visit

* $p < 0.05$

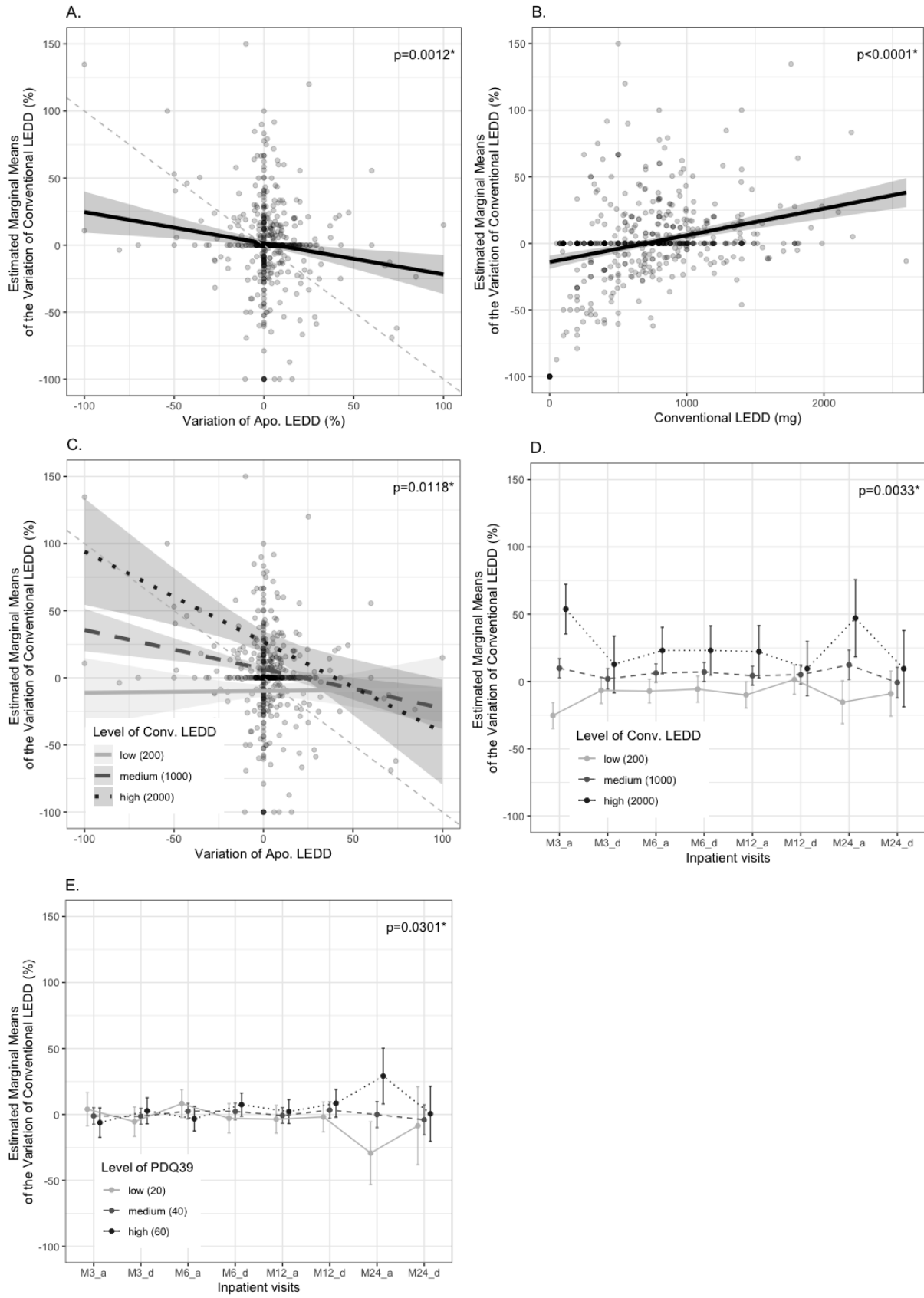


Figure 4: Variation of conventional LEDD during 2-years follow-up

Estimated marginal means of varConv using the linear mixed model expressed as a function of varApo (A), convLEDD (B), the interaction between the inpatient visit and the level of convLEDD (C), the interaction between the inpatient visit and the PDQ-39 score (D), and the interaction between varApo and the level of convLEDD (E).

In (A), (B), and (C), each dot represents varConv for a single patient and visit. In (A), the dashed line represents the equivalence of varApo vs varConv. In (B) and (C), the black full-line represents the regression with the confidence intervals in grey. In (C), (D), and (E), we divided the patients in three groups according to the level of convLEDD (C) and (D), and the PDQ-39 score (E) to illustrate the interactions.

a: admission for the inpatient visit start

d: discharge for the end of inpatient visit

* $p < 0.05$

Table 1: Baseline characteristics

	Patients <i>N=89</i>
Age (y)	64.00 [56.00, 70.00]
Gender (Female)	47 (52.8%)
Duration of PD (y)	11.00 [8.00, 15.00]
UPDRS I	2.00 [2.00, 4.00]
UPDRS II in ON	7.00 [3.50, 12.00]
UPDRS II in OFF	21.00 [15.00, 25.00]
UPDRS III in ON	17.00 [11.00, 25.00]
UPDRS IV	8.00 [6.00, 10.00]
HY in ON	2.00 [1.50, 2.50]
HY in OFF	3.00 [2.50, 4.00]
SE in ON	0.90 [0.75, 0.90]
SE in OFF	0.60 [0.40, 0.70]
MMSE	28.00 [25.00, 30.00]
Conventional LEDD on admission (mg)	1297.50 [973.75, 1490.00]
Proportion of Dopamine Agonists in conventional LEDD on admission (%)	9.0 [0.0, 16.1]

Data are given as Median [1st quartile, 3rd quartile] for continuous variables and as count (percentages) for categorical variables.

Supplementary Table 1: Selection of the variables for the analysis of apomorphine LEDD at baseline with $p < 0.2$.

	p
Gender	0.822
Age	0.087*
Duration of PD	0.047*
UPDRS I	0.975
UPDRS II in ON	0.855
UPDRS II in OFF	0.295
UPDRS III in ON	0.300
UPDRS IV	0.275
HY in ON	0.818
HY in OFF	0.958
SE in ON	0.660
SE in OFF	0.747
MMSE	0.091*
FAB	0.152*
PDQ39	0.313
ASBPD II	0.031*
ASBPD	0.739

Conventional LEDD on admission (mg)	0.135*
Proportion of Dopamine Agonists in conventional LEDD on admission (%)	0.811

P Values were extracted from the simple regression.

Supplementary Table 2: Comparison of baseline characteristics between included and not included patients

	all <i>N=118</i>	Not included patients <i>N=29 (24.6%)</i>	Included patients ¥ <i>N=89 (75.4%)</i>	p ‡
Age (y)	64.00 [57.00, 69.00]	64.00 [58.00, 69.00]	64.00 [56.00, 70.00]	0.528
Gender (Female)	59 (50.00%)	12 (41.4%)	47 (52.8%)	0.393
Age at Start PD (y)	51.00 [44.25, 56.00]	52.00 [48.00, 57.00]	51.00 [43.00, 56.00]	0.197
Duration of PD (y)	11.00 [8.00, 15.00]	10.00 [7.00, 14.00]	11.00 [8.00, 15.00]	0.398
UPDRS I	2.00 [2.00, 4.00]	3.50 [2.00, 5.00]	2.00 [2.00, 4.00]	0.030*
UPDRS II ON	7.00 [3.00, 12.00]	8.50 [2.75, 13.25]	7.00 [3.50, 12.00]	0.614
UPDRS II OFF	21.50 [14.75, 26.00]	24.00 [15.00, 29.50]	21.00 [15.00, 25.00]	0.694
UPDRS III ON	17.00 [10.00, 25.00]	14.50 [8.50, 20.25]	17.00 [11.00, 25.00]	0.226
UPDRS IV	8.00 [6.00, 10.00]	9.00 [7.00, 10.00]	8.00 [6.00, 10.00]	0.574
HY ON	2.00 [1.50, 2.50]	2.50 [2.00, 3.00]	2.00 [1.50, 2.50]	0.174
HY OFF	3.00 [2.50, 4.00]	3.00 [2.50, 4.00]	3.00 [2.50, 4.00]	0.992
SE ON	0.80 [0.70, 0.90]	0.80 [0.67, 0.90]	0.90 [0.75, 0.90]	0.257
SE OFF	0.60 [0.40, 0.70]	0.50 [0.40, 0.60]	0.60 [0.40, 0.70]	0.260
MMSE	28.00 [25.00, 29.00]	27.50 [24.25, 29.00]	28.00 [25.00, 30.00]	0.079
FAB	17.00 [14.00, 18.00]	15.00 [12.00, 17.00]	17.00 [15.00, 18.00]	0.004*
PDQ-39	43.59 [33.97, 51.12]	43.59 [37.18, 51.28]	43.59 [33.97, 50.64]	0.972
ASBPD II	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.309
ASBPD	7.00 [4.00, 10.50]	7.00 [4.00, 11.00]	7.00 [4.00, 10.00]	0.479
No hallucination	118 (100.00%)	29 (100.00%)	89 (100.00%)	
No orthostatic hypotension	118 (100.00%)	29 (100.00%)	89 (100.00%)	
Conventional LEDD on admission (mg)	1286.75 [969.62, 1520.44]	1276.00 [978.62, 1607.12]	1297.50 [973.75, 1490.00]	0.830

Proportion of Dopamine Agonists in conventional LEDD on admission (%)	8.44 [0.00, 15.61]	2.04 [0.00, 9.99]	9.01 [0.00, 16.11]	0.150
Weight (kg)	65.00 [56.00, 76.50]	70.00 [57.50, 74.50]	64.00 [56.00, 77.00]	0.640

Data are given as Median [1st quartile, 3rd quartile] for continuous variables and as count (percentages) for categorical variables.

‡ Wilcoxon-Mann-Whitney test was used to compare groups for continuous variables and Fisher's exact test for qualitative variables.

¥ Included patients were those with no missing data at baseline in Age; Gender; Age at start PD; Duration of PD; UPDRS I; UPDRS II in ON; UPDRS II in OFF; UPDRS III in ON; UPDRS IV; HY in ON; HY in OFF; SE in ON; SE in OFF; MMSE; FAB; PDQ-39; ASBPD; ASBPD II; hallucinations on M0 admission; orthostatic hypotension on M0 admission; conventional LEDD on M0 admission; proportion of Dopamine Agonists in conventional LEDD on admission; proportion of apoLEDD on M0 discharge

Supplementary Table 3: Linear mixed effects model (LMM) results on varApo

	Coefficient \pm se ¥	Cohen's f ²	p
Inpatient visit		0.035	0.0042*
<i>M3_d</i>	6.67 \pm 3.45		
<i>M6_a</i>	-1.56 \pm 3.44		
<i>M6_d</i>	1.41 \pm 3.53		
<i>M12_a</i>	0.94 \pm 3.41		
<i>M12_d</i>	4.29 \pm 3.44		
<i>M24_a</i>	5.88 \pm 4.65		
<i>M24_d</i>	5.49 \pm 4.68		
varConv	0.01 \pm 0.04	0.013	0.0106*
apoLEDD ‡	10.19 \pm 2.68	0.046	<0.0001*
Gender (Male)	0.47 \pm 1.20	<0.001	0.6854
Age at baseline	-0.11 \pm 0.07	0.008	0.0862
Duration of PD at baseline	0.12 \pm 0.12	0.001	0.3199
HY in OFF	0.52 \pm 0.62	0.002	0.3699
Variation of HY in OFF	0.02 \pm 0.02	0.002	0.1537
UPDR SII in OFF	0.01 \pm 0.08	<0.001	0.9055
Variation of UPDRS II in OFF	0.00 \pm 0.02	<0.001	0.9131

UPDRS II ON	-0.08 ± 0.10	0.001	0.4561
Variation of UPDRS II ON	0.00 ± 0.01	<0.001	0.6613
UPDRS III in ON	-0.02 ± 0.05	0.001	0.6466
Variation of UPDRS III in ON	0.00 ± 0.01	<0.001	0.7746
MMSE	0.20 ± 0.22	0.001	0.3473
Variation of MMSE	0.03 ± 0.07	<0.001	0.6714
PDQ-39	-0.02 ± 0.05	<0.001	0.6666
Variation of PDQ-39	-0.01 ± 0.02	0.001	0.5828
ASBPD II	0.09 ± 0.72	<0.001	0.8691
Variation of ASBPD II	0.01 ± 0.01	0.001	0.3183
FAB	-0.34 ± 0.28	0.003	0.2164
Variation of FAB	0.01 ± 0.04	<0.001	0.8451
Interaction between the inpatient visit and varConv		0.032	0.0089*
<i>M3_d</i>	-0.15 ± 0.04		
<i>M6_a</i>	-0.03 ± 0.04		
<i>M6_d</i>	-0.02 ± 0.05		
<i>M12_a</i>	0.00 ± 0.05		
<i>M12_d</i>	0.02 ± 0.05		
<i>M24_a</i>	-0.01 ± 0.06		

<i>M24_d</i>	0.00 ± 0.09		
Interaction between the inpatient visit and apoLEDD		0.011	0.2276
<i>M3_d</i> ‡	-5.47 ± 3.44		
<i>M6_a</i> ‡	-2.66 ± 3.49		
<i>M6_d</i> ‡	-4.15 ± 3.50		
<i>M12_a</i> ‡	-5.01 ± 3.34		
<i>M12_d</i> ‡	-7.74 ± 3.36		
<i>M24_a</i> ‡	-8.34 ± 4.29		
<i>M24_d</i> ‡	-10.25 ± 4.32		
Interaction between varConv and apoLEDD	0.00 ± 0.03	<0.001	0.9697

Coefficients and standard error (se) were extracted from complete GLMMs with all interactions. Because of the interactions in the models, inpatient visit, conventional LEDD, varApo and PDQ39 coefficients are not directly interpretable. Cohen's f2 were calculated using marginal R2.

¥ For the following effect, the reference category (in brackets) was: gender: female; inpatient visit: M3_a

‡ value divided by 1,000 to make the coefficient readable

a: admission for the inpatient visit start

d: discharge for the end of inpatient visit

* p<0.05

Supplementary Table 4: Linear mixed effects model (LMM) results on varConv

	Coefficient ± se ¥	Cohen's f²	p
Inpatient visit		0.006	0.8682
<i>M3_d</i>	5.90 ± 15.60		
<i>M6_a</i>	25.04 ± 14.93		
<i>M6_d</i>	3.53 ± 14.99		
<i>M12_a</i>	3.70 ± 15.24		
<i>M12_d</i>	13.01 ± 15.64		
<i>M24_a</i>	-60.62 ± 23.51		
<i>M24_d</i>	2.72 ± 29.21		
varApo	0.09 ± 0.15	0.019	0.0012*
Conventional LEDD ‡	44.92 ± 7.05	0.092	<0.0001*
Gender (Male)	1.48 ± 2.62	0.001	0.5573
Age at baseline	0.19 ± 0.15	0.003	0.1845
Duration of PD at baseline	-0.29 ± 0.26	0.002	0.2478
HY in OFF	-1.11 ± 1.49	0.001	0.4377
Variation of HY in OFF	0.00 ± 0.05	<0.001	0.9770
UPDRS II in OFF	-0.26 ± 0.20	0.003	0.1799
Variation of UPDRS II in OFF	0.02 ± 0.05	<0.001	0.7116

UPDRS II in ON	0.14 ± 0.25	0.001	0.5595
Variation of UPDRS II in ON	-0.01 ± 0.02	0.001	0.4245
UPDRS III in ON	-0.14 ± 0.13	0.002	0.2736
Variation of UPDRS III in ON	0.00 ± 0.01	<0.001	0.7227
MMSE	-0.02 ± 0.53	<0.001	0.9617
Variation of MMSE	0.06 ± 0.19	<0.001	0.7344
PDQ-39	-0.25 ± 0.26	0.001	0.4310
Variation of PDQ-39	-0.03 ± 0.07	<0.001	0.6938
ASBPD II	2.41 ± 1.72	0.004	0.1453
Variation of ASBPD II	0.00 ± 0.04	<0.001	0.9523
FAB	-0.63 ± 0.69	0.002	0.3448
Variation of FAB	-0.05 ± 0.12	<0.001	0.6908
Interaction between the inpatient visit and convLEDD		0.038	0.0033*
<i>M3_d ‡</i>	-33.21 ± 10.52		
<i>M6_a ‡</i>	-27.18 ± 9.53		
<i>M6_d ‡</i>	-27.96 ± 9.89		
<i>M12_a ‡</i>	-26.08 ± 10.15		
<i>M12_d ‡</i>	-33.43 ± 10.58		
<i>M24_a ‡</i>	-9.28 ± 13.16		

<i>M24_d</i> ‡	-33.65 ± 13.12		
Interaction between the inpatient visit and the PDQ-39		0.028	0.0301*
<i>M3_d</i>	0.46 ± 0.33		
<i>M6_a</i>	-0.03 ± 0.32		
<i>M6_d</i>	0.51 ± 0.31		
<i>M12_a</i>	0.40 ± 0.31		
<i>M12_d</i>	0.51 ± 0.33		
<i>M24_a</i>	1.71 ± 0.56		
<i>M24_d</i>	0.48 ± 0.63		
Interaction between the varApo and convLEDD ‡	-0.38 ± 0.16	0.011	0.0118*

Coefficients and standard error (se) were extracted from complete GLMMs with all interactions. Because of the interactions in the models, inpatient visit, conventional LEDD, varApo and PDQ39 coefficients are not directly interpretable. Cohen's f2 were calculated using marginal R2.

¥ For the following effect, the reference category (in brackets) was: gender: female; inpatient visit: M3_a

‡ value divided by 1,000 to make the coefficient readable

a: admission for the inpatient visit start

d: discharge for the end of inpatient visit

* p<0.05

This study intended to observe medical decisions about CSAI and conventional treatment, in terms of various PD parameters-of-interest. The results suggested that symptom of apathy is considered for the actions on CSAI at initiation, which may also be considered in the selection criteria of potential candidates for a closed-loop system. However, apathy had no significant impact in long-term follow-up, so we can hypothesize that this would not be a parameter of interest for continuous monitoring in an adaptive CSAI. Moreover, to date, there is no known device that enables objective measurement of apathy without human interaction. This study also indicated that no specific parameter-of-interest from PD symptom evaluations with clinical scales, nor patient characteristics had a significant impact on repeated actions in CSAI, and in conventional treatment.

In order to further illustrate the results of this study, the next figures show the lack of association between patients' characteristics and disease scores and varApo (Figure 11), and varConv (Figure 12). Our models revealed that there was no significant effect of gender, age, and duration of PD on varApo nor on varConv. Inpatient visits had no significant effect on varConv. Also, neither the absolute values nor the variation of the UPDRS II in ON, UPDRS II in OFF, UPDRS III in ON, HY in OFF, MMSE, FAB, PDQ-39, ASBPD II had a significant effect on varApo nor on varConv (Supplementary Tables 3 and 4 of this study's manuscript). In Figure 11 and Figure 12, each dot represents varApo and varConv respectively, for a single patient and visit, and the black full-line represents the regression with the confidence intervals in grey (a: admission for inpatient visit start, d: discharge for end of inpatient visit).

Our results are a first insight on the organization of care for advanced PD patients with CSAI therapy. The findings may trigger new thinking about the process of pump initiation and its longstanding use. To complement those results, the reverse impacts of PD features on the adaptations of conventional treatments and CSAI may be studied in the same cohort of patients. Also, it might be of interest to consider further evaluation of the link between conventional

LEDD and apomorphine LEDD as we did not find an exact equivalence in their adaptations across the two years of follow-up. The admitted equivalence in pharmacological dosage might not completely match the clinical equivalence of the two therapies when outcomes are measured in patients (Tomlinson et al. 2010).

This study did not find a parameter-of-interest for adaptive CSAI. However, the PD parameters considered in the analysis were scores from clinical scales. Another type of measurement, such as BWS monitoring could point out different parameters-of-interest that might impact the actions on treatment. Further investigation to better understand how BWS monitoring results impact CSAI actions is needed.

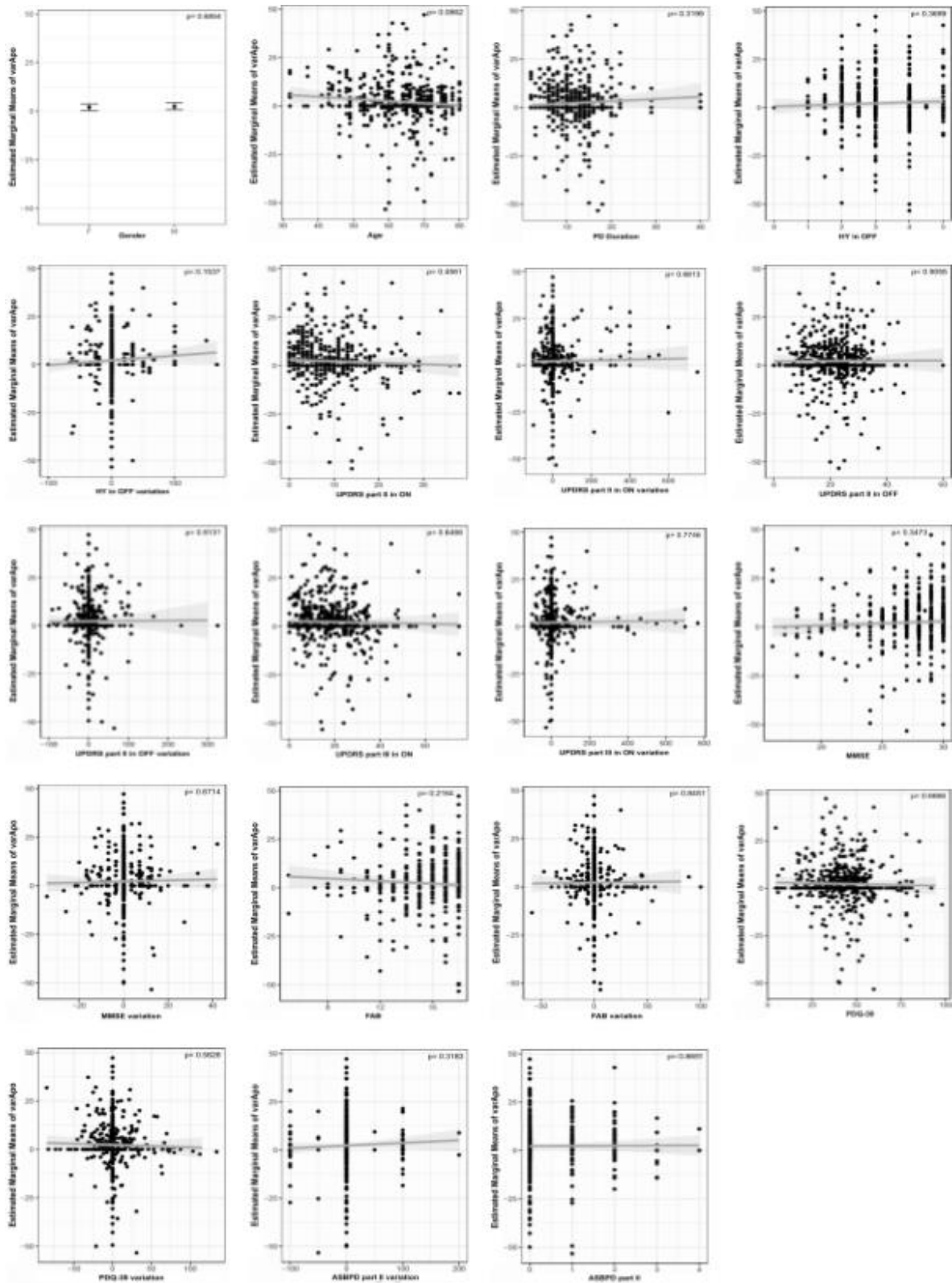


Figure 11: Estimated marginal means of varApo
Using the linear mixed model expressed as a function of parameters that did not significantly influence it

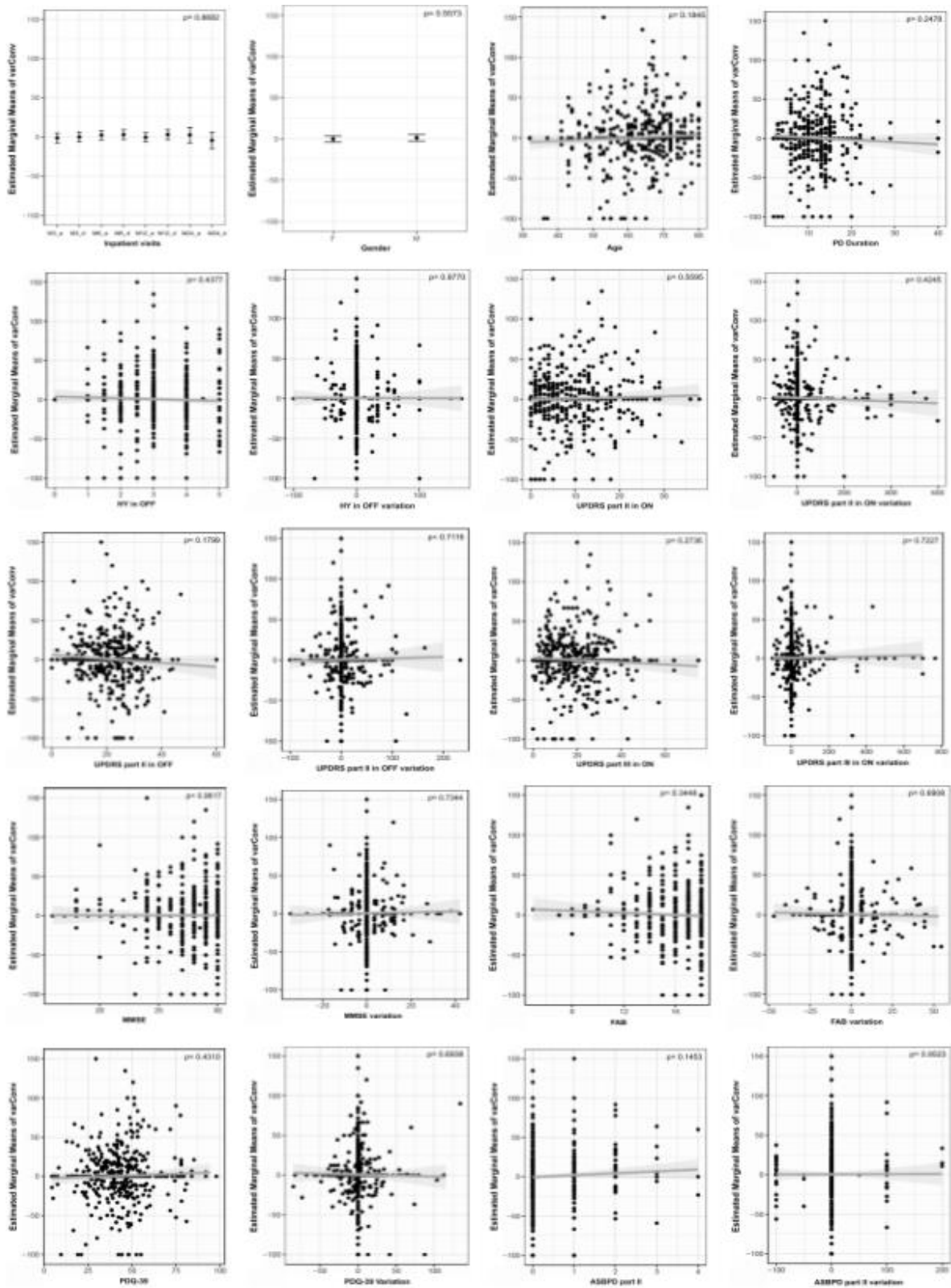


Figure 12: Estimated marginal means of varConv

Using the linear mixed model expressed as a function of parameters that did not significantly influence it

2.3 Analysis of treatment trajectories as a function of PD symptoms

In this study, we expose the preliminary results of the analysis of the trajectories of four treatment features in patients with CSAI across two years of follow-up.

The objective of this analysis was to study the patients' characteristics or disease scores that could have an influence on the trajectories of treatment over two years (*i.e.*, increase, decrease or stabilization of a treatment parameter).

We used the same data that is described in the Methods section of the study presented above and in total included 120 patients in the analysis. Patients' characteristics are available in Supplementary Table 1 of the previous study. We selected five treatment features whose trajectories would be explained by a score value at a visit and its difference compared to the previous visit. Those treatment features are: proportion of apomorphine LEDD compared to the total LEDD (%apo), proportion of apomorphine at night (%apo night, which highlights patients who receive apomorphine infusion only during daytime or at night too), total LEDD, and mean dose per intake (regarding oral treatment, total dose (mg) per day divided by the number of intakes per day).

To study the longitudinal evolution of the treatment parameters cited above, we performed a Latent Class Linear Mixed Model (LCLMM) (Proust and Jacqmin-Gadda 2005) for each of them to investigate heterogeneous trajectories. LCLMM first identifies G classes of subjects who share a similar trend of evolution in each of the treatment features (%apo, %apo night, total LEDD, and Mean Dose per Intake), and then LCLMM compares the classes. In order to find an adequate and clinically relevant number of classes G , we computed the model from one to five classes and selected the one which minimized the Bayesian Information Criterion. Mean of posterior probabilities, as well as percentage of posterior probabilities higher than 0.7 were computed. The evolution of %apo, %apo night, total LEDD, and Mean Dose per Intake was modelled by the interaction between classes and visits. Then, to compare classes according to

demographic items and clinical scores, we performed a Kruskal-Wallis test for continuous variables and Fisher’s exact test for qualitative variables. Pairwise Wilcoxon–Mann–Whitney tests for continuous variables and pairwise Fisher’s exact tests for qualitative variables were performed to investigate pairwise comparison using the Benjamini-Hochberg method to correct for multiple testing.

Statistical analyses were performed using R 4.0.2. Package lclmm (version 1.9.2) was used to perform LCLMM.

The classes created by the model according to the direction of each treatment feature are detailed in Supplementary Tables 1, 2, 3, and 4 of Supplementary Material II. Figures 13, 14, 15, and 16 show the trajectories of the five treatment features studied along the two-year follow-up at each visit (M0, M3, M6, M12, and M24) admission (a) and discharge (d) (in graphs A, full lines in the color of each treatment feature represent the regression with the confidence intervals in transparency; in graphs B, the black lines are the individual trajectories of the representatives of the classes).

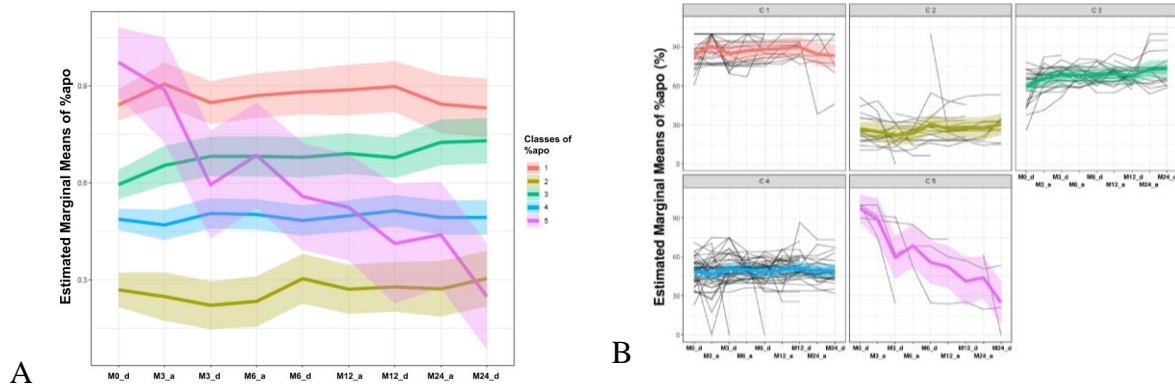


Figure 13: Classes of patients for %apo (proportion of apomorphine in the total treatment)

The five groups created for %apo included 22, 17, 25, 44, and 4 patients, respectively (Figure 13 A and B, and Supplementary Table 1 in Supplementary Material II). The first class (Class 1) was characterized by high (around 90%) and steady %apo along the two-year follow-up.

Class 2 was characterized by low (around 25%) and steady %apo along the two-year follow-up. Class 3 and Class 4 represented intermediate %apo, with an increasing trend for Class 3 and stabilization at around 50% for Class 4. Finally, Class 5 was marked by a decrease of %apo along the two-year follow-up but with a limited number of representatives. Patients in Class 1 had a significantly shorter duration of PD compared to Class 2, Class 3, and Class 4 ($p=0.003$), and significantly greater FAB scores, *i.e.*, better performance in cognitive functions, compared to Class 2 and Class 4 ($p=0.014$).

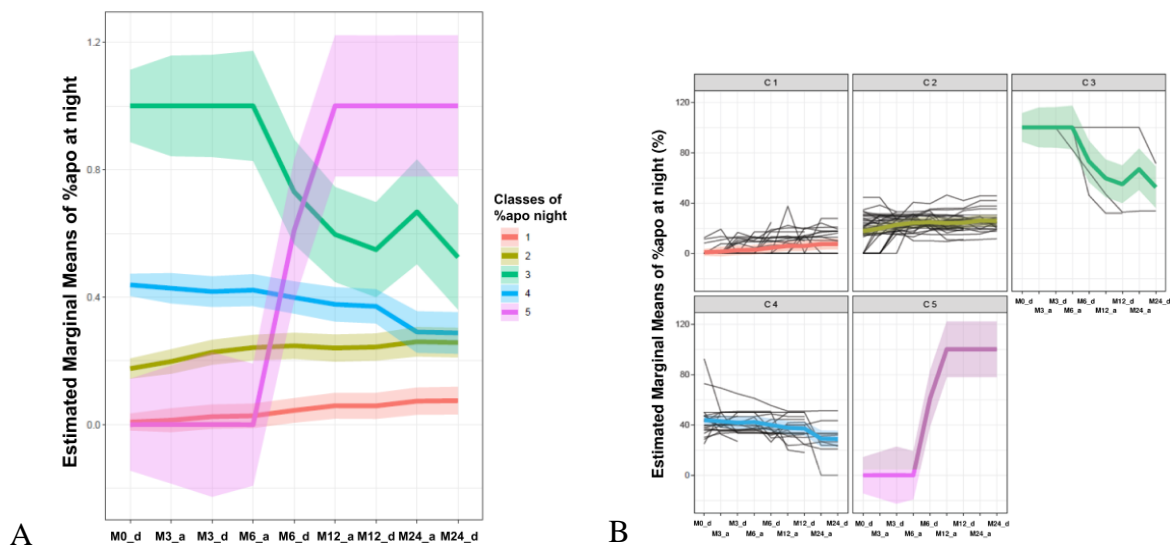


Figure 14: Classes of patients for %apo night

(proportion of apomorphine received at night in the daily delivery of apomorphine)

Regarding %apo night (Figure 14 A and B, and Supplementary Table 2 in Supplementary Material II), the five classes comprised 41, 42, 3, 25, and 1 patient, respectively. Class 1 showed a small augmentation tendency along the two-year follow-up with very low %apo night (between 0% and 10%), meaning that 34% of the patients in this analysis had similar small proportions of their daily apomorphine delivery at night. Patients of Class 2 represented 35% of the population and they seemed to have a comparable tendency of %apo night augmentation at greater levels (around 20% to 30%). On the contrary, patients in Class 4 were likely to see

their %apo night decrease along the two years after CSAI initiation (from around 45% to 30% of their total apomorphine delivery per day). Classes 3 and 5 enclosed too few patients to be generalized but their representatives respectively experienced an important decrease of their %apo night after admission of M6, and an abrupt increase of %apo night between admissions of M6 and of M12. No significant differences between the classes could be highlighted by this analysis.

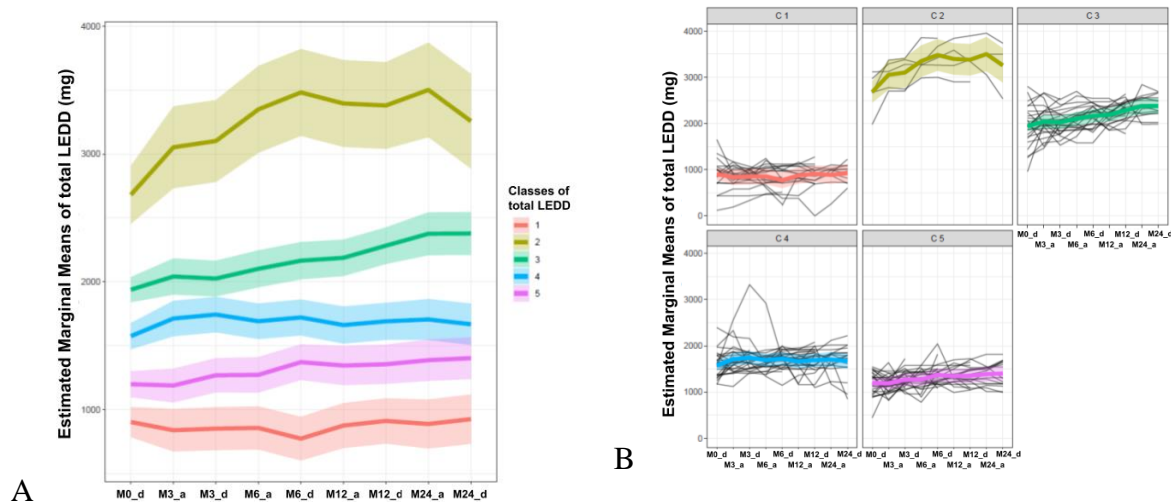


Figure 15: Classes of patients for total LEDD

(in mg)

The study of total LEDD revealed five independent classes (Figure 15 A and B, and Supplementary Table 3 in Supplementary Material II) that included 20, 5, 28, 29, and 30 patients, respectively. Class 1 included patients with relatively stable total LEDD across the two years and below 1000 mg. Class 2 comprised patients with the highest total LEDD (above 2500 mg). Those patients seemed to experience a consequential increase of total LEDD from M0 to discharge of M6. Then, they were likely to stabilize at around 3500 mg (with a short decrease at M24, but that could be explained by the reduction of the patient number at this visit). Patients in Class 3 had a clear augmentation of total LEDD from around 2000 mg to 2500 mg during the two years of follow-up with CSAI. Class 4 and Class 5 converged to 1500 mg of

total LEDD. Especially, Class 5 showed a small and continuous increase along the two years from initiation of CSAI. There were no patient characteristics or PD score that could significantly differentiate the classes from each other.

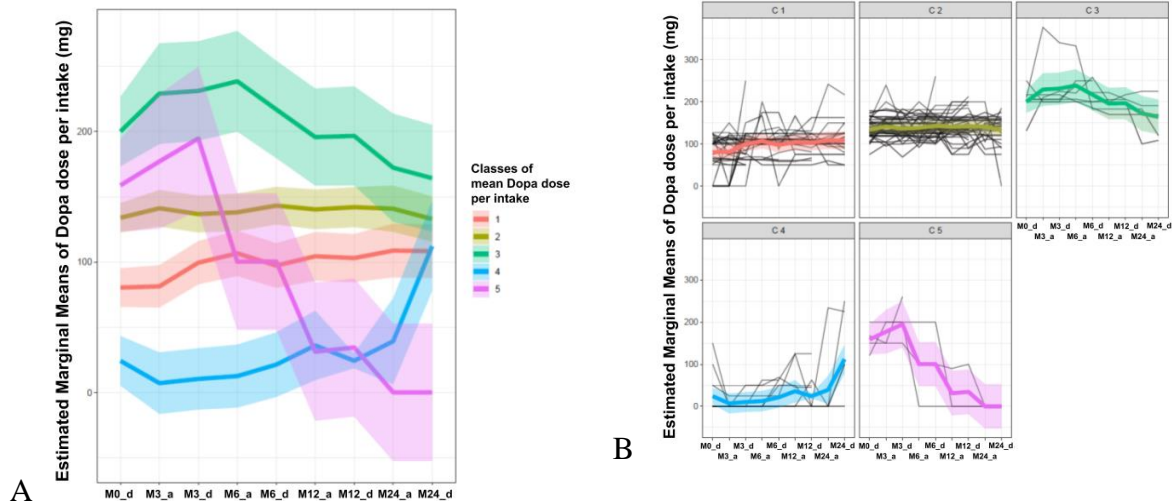


Figure 16: Classes of patients for mean dose per intake (in mg)

The trajectories of the mean dose of levodopa per intake was divided into classes enclosing 37, 49, 7, 15, and 4 patients, respectively (Figure 16 A and B, and Supplementary Table 4 in Supplementary Material II). Patients of Class 1 received a mean dose per intake of around 100 mg, which was increased at M3. Patients of Class 2 received more levodopa per intake, but this amount seemed relatively steady along the two years after CSAI initiation (around 140 mg). Class 3 experienced an initial increase of the mean dose per intake during the six first months after CSAI initiation, and then the reduction appeared constant until the end of the follow-up. However, only a few patients represented this class. Class 4 included patients with low mean dose per intake at the beginning of the follow-up (until M6), but they experienced a strong increase of this mean dose at M12 and M24. Class 5 included only a few patients whose mean dose per intake seemed to decrease drastically at each visit during the two-year follow-up. Class

1 and Class 4 were significantly different regarding the score in UPDRS part IV ($p= 0.041$), patients of Class 1 had a lower score, *i.e.*, less severe PD complications.

In the retrospective study, we did not find any significant impact of a specific PD score on the adaptations of either conventional or CSAI therapies (Virbel-Fleischman, Houot, et al. 2020). By using the latent classes approach to study characteristics of a treatment's evolution across the two-year follow-up, we showed the impact of the duration of PD and the cognitive function (FAB score) on the various trajectories of the proportion of apomorphine in the total LEDD. The shorter the progression of PD, the greater and more stable the %apo. Moreover, high cognitive performance may explain the assignment to a certain level of %apo that would remain stable for two years. Further analysis of the classes of the different treatment features may be helpful to obtain a deeper interpretation. This complementary study also showed that the score in UPDRS part IV may explain the evolution of the mean dose per intake along the two years after CSAI. However, we did not study this treatment feature in particular in the retrospective study. Moreover, the interpretation of the classes is limited by the number of patients per class, and the nature of the trajectories *per se*. Indeed, we have seen in the retrospective study that the increase in apomorphine LEDD due to the initiation of CSAI, in parallel to the decrease of conventional LEDD, favors a global and slow increase of total LEDD during the two first years with CSAI. We also observed that conventional treatments adaptations were not dependent on the inpatient visit during the follow-up. Only CSAI adaptations were different from one visit to another. Thus, maybe the profiles of adaptations were not sufficiently clustered to describe clear treatment trajectories, as we expected (*i.e.*, increase, decrease and stabilization). Further, perhaps the clinical parameters that we used to find any description of the trajectories were not adequate and other signs may be more appropriate (*e.g.* adverse events of CSAI, autonomic disorders, *etc.*). Several perspectives may help expand the preliminary

discussion about these preliminary results. First, the number of patients included in this study might be augmented. Second, we may restrict the model to create less classes from the treatment trajectories, forcing the number of patients per class to be enlarged, but this option is at risk of creating undefined classes gathering different trajectories. Third, we used the patients' characteristics and PD scores obtained at CSAI initiation, but further analysis should be performed to determine if the evolution of those characteristics and scores may define the evolutions of treatment trajectories. However, patients may experience various evolutions of symptoms and different trajectories for each treatment feature, which may engender multiple possible interpretations of therapeutic strategies according to each particular patient's characteristics. Besides, this new approach may complete the retrospective study we performed, in which we could not find an effect of any disease parameter nor their variations on treatment variations.

The preliminary results do not enable a conclusion on the potential tuning of the adaptive CSAI in the long-term according to a specific parameter of interest. Furthermore, as previously, the monitoring of other parameters of interest by BWS might be explored to obtain further information about the functioning of a hypothetical closed-loop.

2.4 Increased objectivity could support actions on treatment, but where do we stand regarding BWS adoption?

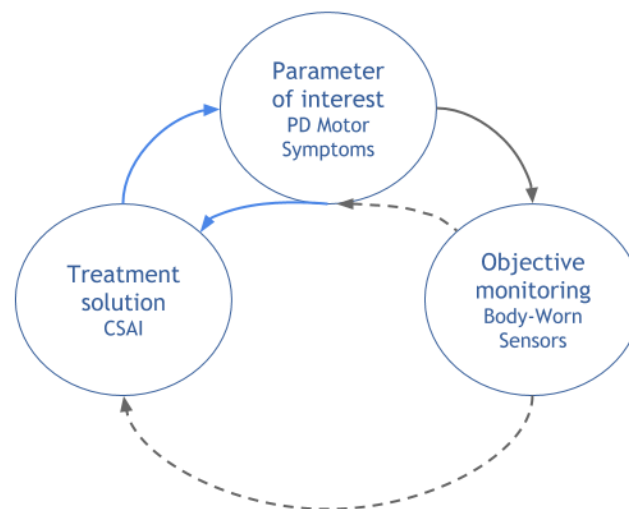


Figure 17: Scheme of adaptive CSAI based on BWS monitoring of motor symptoms in line with a closed-loop system. Dashed lines are links uncovered by the literature. Blue lines represent the links we have studied in this section of the manuscript

We depicted a first link between two elements of a hypothetical closed-loop: CSAI and PD motor symptoms (Figure 17). Beyond any doubt, CSAI has a positive impact on PD symptoms according to our results and in line with a large body of literature. The actions on CSAI were influenced by the patient's apathy at the initiation of the treatment, but no other parameter of interest could be found during the continuous follow-up. This study remarkably questions the absolute necessity of all inpatient visits in our cohort of patients, and thus, the organization of care. Given the patient's symptom severity, reaction to CSAI therapy and careful observation of adverse events, all hospitalizations might not be mandatory except the first three months which seem crucial. The supervision of such a defined population of PD patients may be performed with regular outpatient visits and at home follow-up. Thus, reinforced remote care might be explored to reduce inpatient stays, and which may decrease the

hospital burden and health expenditures. BWS monitoring could be an effective tool to keep a close watch on symptom evolution and support actions on treatment. However, are patients and health professionals ready to use such technique in their daily-life and as standard practice?

This will be the interest of the next study.

3. A look at patient and health professional readiness regarding BWS usage

We previously described objective monitoring with BWS and the potential beneficial impacts in clinical practice as they can accurately measure the motor symptoms of PD patients. We are now interested in the effect that BWS produces in users, *i.e.*, their perception of the technology and available devices. The majority of the conclusions on the acceptability and usability of BWS were until now informal (Del Din et al. 2016), sometimes coming from succinct questions to patients or results from usability scales. We focused our work on the user experience, taking into account the patient and the healthcare professional (HP). The acceptability to patients in wearing a sensor for continuous recording of their movements was collected as a secondary purpose (Lopane et al. 2015; Silva de Lima et al. 2016; 2017). Devices were rarely designed and built according to the acceptability of the ergonomics or the opinion perceived by users (Cancela, Pastorino, Tzallas, et al. 2014; Fisher et al. 2016; Ferreira, Godinho, et al. 2015). However, the addition of BWS in the standard follow-up of PD requires patients and HP to conveniently appropriate the new device. Patient compliance may be associated with comfortable and easy-to-use devices that utilize a justified number of sensors and locations on the body. Also, patients may tolerate wearing a device in their daily life if the results provide a meaningful improvement in their quality of life, and in parallel, their wellbeing might be increased by their own involvement in care engendered by wearing such device (van Uem et al. 2016). Moreover, patient compliance is important for clinicians to be confident in the results of monitoring that may serve a decision on treatment. Importantly, the incorporation of a closed-loop system with CSAI and BWS in the daily life of patients may be a relevant solution if patients agree on the inclusion of a device for objective measurement in addition to

the apomorphine pump. From this perspective, we decided to conduct a qualitative study on the perception of BWS in patients and HP.

3.1 Body-Worn Sensors for Parkinson’s disease: a qualitative approach with patients and healthcare professionals [Submitted] (Virbel-Fleischman, Rétory, et al. 2020)

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Running title: Wearables: users perspectives in Parkinsonism

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List of abbreviations:

ATT: Attractiveness

BWS: Body-Worn Sensors

HP: Health Professionals

HQ: Hedonic Qualities

HQ-I: Hedonic Qualities - Identification

HQ-S: Hedonic Qualities - Stimulation

PD: Parkinson’s disease

PQ: Pragmatic Qualities

SUS: System Usability Scale

UX: User Experience

ABSTRACT

Background: Body-Worn Sensors (BWS) provide reliable objective and continuous assessment of Parkinson's disease (PD) motor symptoms, but their implementation in clinical routine has not yet become widespread. Users' perceptions of BWS have not been explored.

Objectives: This study intended to evaluate the usability, user experience (UX), patients' perceptions of BWS, and health professionals' (HP) opinions on BWS monitoring.

Methods: A qualitative analysis was performed from semi-structured interviews conducted with 22 patients and 9 HP experts in PD. Patients completed two interviews before and after the BWS one-week experiment, and they answered two questionnaires assessing the usability and UX.

Results: Patients rated the three BWS usability with high scores (SUS median [range]: 87.5 [72.5 - 100]). The UX across all dimensions of their interaction with the BWS was positive. During interviews, all patients and HP expressed interest in BWS monitoring. Patients' hopes and expectations increased the more they learned about BWS. They manifested enthusiasm to wear BWS, which they imagined could improve their PD symptoms. HP highlighted needs for logistical support in the implementation of BWS in their practice. Both patients and HP suggested possible uses of BWS monitoring in clinical practice, for treatment adjustments for example, or for research purposes.

Conclusion: Patients and HP shared ideas about the use of BWS monitoring, although patients may be more likely to integrate BWS into their disease follow-up compared to HP in their practice. This study highlights gaps that need to be fulfilled to facilitate BWS adoption and promote their potential.

Keywords: Parkinson's disease, Wearable sensors, Ambulatory monitoring, Qualitative research, Perception, Patients-centered, Expert opinion

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting about six million people worldwide [1]. In PD, the loss of dopaminergic neurons results in the three main motor symptoms that are the hallmarks of the disease: akinesia, resting tremor and hypertonia. Other symptoms, due to dopaminergic and non-dopaminergic lesions, include gait and balance deficits and a wide spectrum of non-motor symptoms. Currently, PD treatment is symptomatic and consists of dopaminergic substitution. Therapeutic strategies depend on the patients' profiles and disease severity [2,3]. Although these strategies are personalized all along the care pathway, assessment of symptoms that could drive treatment adaptation, either during outpatients visits or hospitalizations, is highly challenging, particularly when motor fluctuations and dyskinesia occur [4]. A mismatch may exist between the physician's assessment and the patient's perception of his/her pathology [5]. This may be because of gaps in the patient's knowledge of symptomatology or memory biases [6] or because of stress induced by the medical environment which may cause, for instance, a "white-coat effect" [7] that decreases the chances of observing specific symptoms. Among the different PD scales scoring the severity, the patient's diary allows for an assessment of symptoms every 30 minutes [8]. Still, it is subjective, and compliance might be too low to provide reliable information [9]. In parallel, hospitalizations are costly and not ecological [10,11]. Facing these limitations, as suggested by Odin et al. [12], PD management could be improved by introducing Body-Worn Sensors (BWS) into PD care pathways as technology-based monitoring in ecological conditions.

BWS are wearable systems embedded with movement analysis algorithms to record the body's activity. They are usually composed of triaxial accelerometers and sometimes triaxial gyroscopes, which capture displacement and speed and translate characteristics of movements into specific symptoms of PD. They allow continuous, quantitative and real-life monitoring of motor symptoms [13–15]. BWS can be worn on the wrist, the ankle, or the trunk, and can be used for several days in the patient's home without medical supervision. Studies have shown that these systems provide relevant information on the driving states of PD in free-

living conditions [16]. They can support clinical evaluation of the symptoms experienced daily to assess disease evolution and facilitate its understanding [17–21].

Ambulatory assessment of motor symptoms with BWS may be useful for PD management, although its clinical relevance is not yet demonstrated. However, more information is needed before fostering routine adoption of this technology [22]. Together with data regarding the clinical efficacy of BWS-based care, the assessment of the user experience (UX), from both the patients' and healthcare professionals' perspectives, is essential [23]. Currently, only a few independent user-centered investigations have been conducted, and knowledge of the users' opinions of BWS and their usability and attractiveness is still missing. This qualitative study intended to explore PD patients' and health professionals' (HP) perceptions of BWS technology, focusing on:

- BWS usability and patients' UX
- PD patients' opinion of BWS
- Neurologists' and nurses' opinion of BWS

METHODS

Participants

Participants were recruited to take part in the study voluntarily. Participants signed an informed consent and they could withdraw from the study at any time, avoid answering a question, or stop the interview. The study focused only on participants' perceptions and the patients included were followed in routine care. No data collected during this study was used to change the care delivered to the patients. The study took place from January to November 2019 and approval from the Review Board was waived.

Patients

Inclusion criteria for patients were a diagnosis of PD without dementia and their presence at the hospital once a week for routine care visits. Semi-structured interviews were conducted with patients who also completed two questionnaires at the end of their participation. Patients were divided into three groups according to the BWS worn.

The procedure of participation included (Figure 1):

- the first contact at the hospital during a normal care visit for recruitment and interviews planning;
- the first interview, held at the hospital according to an interview guide, allowing patients to first handle one BWS, that was selected before interview depending on the BWS availability at the time of inclusion;
- a one-week experience with the BWS, at the patients' homes without supervision; and
- the second interview, held at the hospital according to an interview guide and questionnaire completion.

Health professionals

Neurologists and nurses specializing in PD were selected from a listing of two Movement disorder expert centers in the Paris region to be invited to participate. The recruitment ceased when the sample size reached 9 HP. Semi-structured interviews were conducted with six neurologists and three nurses specializing in PD. The procedure for participation for those 9 HP included (Figure 1):

- the first contact by phone for recruitment and interview planning; and
- an interview held at the hospital according to an interview guide.

Material

The selection criteria for BWS were the possibility to obtain objective and continuous monitoring of PD motor symptoms at the patients' homes without medical supervision and the availability of sensors (CE mark) at the time of the study.

Three different BWS were selected for this experiment:

- BWS a: The PKG Watch (Global Kinetics Corporation, Australia) is a wrist-worn sensor installed on the most affected side of the body 24 hours per day. No specific handling is needed by the patients during home monitoring. Reports of symptoms show severities of bradykinesia, dyskinesia and motor fluctuations, and tremor and immobility presented as graphs and quantitative scores [24–27].

- BWS b: Kinesia 360 (Great Lakes NeuroTechnologies Inc., USA) is a set of two sensor bands worn on the wrist and the ankle of the most affected side of the body during waking hours. Once at home, the patient must install and remove the sensors and start and stop the monitoring every day, thanks to a dedicated Smartphone app. Sensors are charged, and data are downloaded each night. Reports of symptoms show probabilities of appearance and severity of slowness of movement, dyskinesia, tremor, as well as mobility data (e.g., time with gait, time at rest, arm swing percentage) numerically [28–31].
- BWS c: STAT-ON (Sense4Care, Spain) is a sensor-belt worn around the waist during waking hours. Patients need to install and remove it each morning and evening. The sensor is charged at night. The results of monitoring show a summary of motor symptoms with ON, OFF and intermediate states appearance across days as well as dyskinesia, freezing of gait and falls. An extended version of the report shows further details on motor states, mobility and gait parameters (e.g., stride fluidity, step length, cadence, energy expenditure) [18,32–34].

Semi-quantitative approach: usability and user experience of BWS to patients

The usability of BWS was studied with the System Usability Scale (SUS) [35]. The respondents rated their agreement with ten sentences on a 5-point Likert scale. The scores ranged from 0 to 100, with higher scores indicating greater agreement. The adjective ratings of Bangor et al. [36] was used to describe the categories of scores.

BWS UX was studied using the AttrakDiff questionnaire [37,38], which assesses the interaction between the user and the product according to hedonic (HQ) and pragmatic qualities (PQ) described using 28-word pairs measured on a 7-point Likert scale. HQ represent the emotional component of the interaction, and PQ embody the behavioral consequences of the interaction. They both independently play a role in the assessment of product attractiveness. Results are presented as median and [minimum; maximum] values.

Phenomenological approach: UX and opinion on BWS

We applied a phenomenological approach [39] to understand lived experiences and perceptions of patients and HP. Recruitment ceased after the sample sizes of each group were judged appropriate according to previous related studies [40]. Indeed, Morse et al. noted that six to ten participants could be representative of the population of interest. Semi-structured interviews were conducted between the participant and the interviewer, with specific guides for patients and HP, to describe the individuals' conceptions of BWS while guaranteeing a common frame for investigation within all participants [41].

Data collection

Interviews with all participants were audiotaped and transcribed. Participants were prompted to answer frankly and describe their feelings and experiences as they live them. Dialogues evolved naturally following the interview guide to ensure that each topic is addressed. We ensured that interactions with participants were free of any preconceived ideas, as detailed by Wojnar and Swanson [42], and, at the beginning of the second round of interviews, we checked the interpretations of claims patients made during the first interviews. After each interview, the participants validated a summary of the interviewer's understanding of their responses.

The first round of interviews intended to gather the general perspectives of naive participants on BWS (60 - 90 minutes), and the second round of interviews focused on their experiences with the device to examine the UX (30 - 60 minutes) [43,44]. The interview of HP (20 - 60 minutes) was divided into two parts. One first part allowed a general discussion on BWS before their actual demonstration. The second part involved a more specific analysis of BWS monitoring use.

Data analysis

We used NVivo 12 software (Qualitative Data Analysis Software from QSR International [45]) to analyze and standardize the data of the participants' claims to facilitate their interpretation. We applied a four-step approach from the commonly adopted phenomenological method inspired by Giorgi [46,47]:

- Reading of the transcripts to form the first impression (naive understanding);

- Coding of each sentence with NVivo software according to a structural analysis;
- Reviewing of the codes with a comprehensive understanding to look for commonalities and differences following a back and forth movement between the original text and the codes' categories;
- Disclosure of the descriptions based on the codes' categories for patients and HP.

Descriptions of results reflect the participants' most significant perceptions of BWS [48]. One researcher designed the interview guides, interviewed participants, and conducted the qualitative analysis. An external neuropsychologist researcher who selected two interviews with one random patient from each of the three groups cross-checked the codes.

RESULTS

Patients

Twenty-two patients were recruited for this study: 7 with BWS a, 8 with BWS b, and 7 with BWS c. Patients' characteristics are described in Table 1.

BWS usability and UX

Each BWS was appraised by seven patients using the SUS and the AttrakDiff questionnaires (one missing data). No correlation was found between age or disease duration and the SUS and AttrakDiff scores (Supplementary Table 2).

SUS

According to the SUS results, the global usability score for BWS is 87.5 [72.5; 100] (median [range]). The three BWS were assessed as "excellent" to "best imaginable" usability (all scores were above 72.5 on the 100 point scale). SUS scores of BWS a, b, and c were comparable: 90 [77.5; 97.5], 87.5 [72.5; 92.5] and 95 [82.5; 100], respectively.

AttrakDiff

The four categories of the AttrakDiff questionnaire were assessed positively. Global scores for the three BWS regarding attractiveness, PQ, identification of the user to the BWS and stimulation by the BWS to the user were respectively (median [range]): 1 [-3; 3], 2 [-3; 3], 0 [-3; 3] and 2 [-3; 3]. The rating of the three BWS was positive for 84% of all AttrakDiff items, all

categories combined. Figure 2 shows that the three BWS yielded independently very similar results for each AttrakDiff dimension.

Phenomenological analysis

According to the two questionnaires and the phenomenological approach analyses, the three groups of patients were equivalent, and the patients' descriptions allowed us to make general conclusions on BWS monitoring.

General opinion

Before this study, 20 out of the 22 patients had not heard of BWS. Finding a new avenue to help patients with PD was the driving force of volunteering, as a majority of patients expressed. The progress inspired by the new term "BWS monitoring" was perceived as positive and the objectives attractive ("Carrying out this type of investigation is very serious."). Patients developed creative thinking about sensors, and many questions emerged from their reasoning linked either to their interests in the device or to device functioning (Table 2). During the first interview, as shown in Table 2, the expressions used before having seen the BWS reflected positive feelings, interests, expectations, and hopes. Negative feelings, such as apprehensions or doubts, were little expressed.

All 22 patients expressed interest in BWS monitoring. The usefulness of the tool triggered expectations and hopes for disease follow-up: "I think that it could replace the diaries which are complicated to fill, I could show that to the doctor instead of the sheets", "it would help manage everyday activities". All patients said the device would not be a problem in their daily life before and after the use ("normal", "trouble-free", "without any issue", the device was "simple", "easy"). Still, 11 patients mentioned imagined or lived constraints before use and 12 patients after the one-week use. The patients expressed little apprehension of using the BWS, which was confirmed by the one-week use when only two patients manifested apprehension before having seen the device, ten patients after seeing it ("will I be able to use it correctly?", "how should it be done?"), and eight patients after using it. Patients were increasingly enthusiastic about its use in PD follow-up (enthusiasm expressed by seven patients before being introduced to the device, 15 before use, and 19 after use). Patients' curiosity also

increased throughout their discovery, as one patient expressed being curious at the beginning of the first interview versus nine at the end of the second one. Compared to those positive elements, the negative a priori conveyed during the first interview were minor: three patients had negative preconceptions before having seen the device, and 13 before using it.

The physical characteristics and handling of BWS were trivialized ("aesthetically simple", "no problem"). Nevertheless, the device outlook unveiled slight disappointment for four patients and six patients were disillusioned by the device use. Only four patients considered social embarrassment before use. However, they all discussed it during the second interview, although only nine patients expressed the wish that the device should not be visible. For example, the ankle bracelet of BWS b regularly reminded people of the electronic parole bracelets.

Finally, despite specific and individual concerns (wish to leave the device unseen and difficulties in hiding it efficiently, 16 patients expressed slight discomfort or device-related error after use), all patients provided good feedback ("it was a normal week", "I forgot I had it", "everything was fine", "if it helps then we don't care that it could interfere"). A solution was rapidly found after any device-related discomfort was felt. These minimal disturbances have not been classified by the patients as affecting their opinion of the device and its overall ergonomics. In rare cases, patients required help with body placement. Those moments brought about design improvement suggestions to make the wearing even more practical and closer to an everyday object. Indeed, except the BWS a, which does not require specific handling, patients may have to organize their activities several times a day to install/remove the device, or to avoid getting it wet. Eight patients pointed out the feeling of being observed or even spied on. They wondered about privacy and what would be recorded (intimate moments, toilet, *etc.*): "We ask ourselves the question, it's a bit embarrassing, then we move on and we keep on wearing, we forget", "I removed it to go to the toilet even if I suspected that it was not important for you". Those patients declared that they did not change their behavior. However, besides those thoughts, according to their story, six patients changed their behavior at some point for a short time (extra use of the arm wearing the device, additional time awake,

etc.). Those patients explained that this change was not disturbing. To the question “have you changed your behavior while wearing the device?”, five patients answered yes after consideration. Finally, patients justified the behavior change to improve the monitoring to provide the necessary information, which was not bothersome, considering the possible gain. After the one-week experience, 17 patients had a positive, and 5 had a neutral experience with the BWS use. In addition, 17 patients felt concerned about BWS monitoring other than for this study. Quotations from interviews that illustrate those results are presented in Supplementary Table 1.

Suggestions for use

Suggestions for use were based on the patients’ hopes that BWS monitoring will answer their demands and needs. For instance, according to their experiences with the device and their expectations, patients were able to suggest specific schemes for using the device during their PD follow-up (timing and frequency of monitoring, additional monitoring, extra involvement of the patient, *etc.*) or new ways of using it (other types of measurements, such as cardiac rhythm or other pathologies, for example).

The patients’ enthusiasm increased their interest in attaining a better life with the disease (*i.e.*, decrease the symptoms). According to 19 patients, clinicians would benefit from patients wearing the devices, as they would be able to adjust the treatment according to the results of BWS monitoring, “If it comes out of the charts, maybe it will allow the doctor to balance the treatment during the day differently. Maybe it will be an effective aid to the doctor”, “it could be useful to me, to adapt the treatment to adapt it more finely than it is”, “during the visit, if we do not remember correctly, I imagine that one can very quickly be mistaken in medication”. Some of them assumed that they could even individually adapt their timings of medication intakes according to the monitoring results. Still, all patients agreed on the important role of physicians in changing the treatment parameters. Eighteen patients felt the need to know more about their symptoms and 19 expressed the interest to get the results, either to justify the monitoring or their feelings to the physician (and then improve the discussion), according to 17 patients, or to better understand their disease, according to 16 patients (“I didn’t realize when I had

dyskinesias. People had to tell me...I didn't see, well I didn't feel. For example, legs, arms, I didn't realize. It helps people to realize. And it seems that there are also people who do not differentiate between symptoms and dyskinesias; for these people, it can be useful too.”). For 18 patients, the general exchange during consultations was incomplete because they could not have the time to discuss everything they wanted. In parallel with this, 11 and 9 patients were not satisfied with their treatment and PD follow-up, respectively, at the time of the study. Twelve patients also thought about research (“we could compare the benefits of different treatments, for example”) and the advantages of BWS monitoring for PD knowledge (“when we understand what is happening, we can act”). Finally, all the patients appreciated the advantages of using the device, either through its direct influence on symptoms management or advances in research.

Health professionals

The nine HP were working part-time or full time in a movement disorder expert center. The three nurses and three of the six clinicians were women. Seven HP knew about BWS monitoring before the interview. Only two of those were aware of other BWS than the BWS a.

Phenomenological analysis

As none of the HP had used BWS monitoring before the study, the discussion focused on the practice. The presentation of the three BWS at mid-interview provided a general overview of the existing systems. HP's perceptions of each BWS and the different resulting reports, as well as device-specific suggestions of improvements, were not the purpose of this study so the information is not detailed here.

General opinion

A significant interest in BWS monitoring was highlighted by all HP. At the end of the interview, all HP had expressed enthusiasm to use this new technology for PD, showing positive and negative perceptions that were balanced. The attraction was driven by a conceivable beneficial evolution of medicine (“I think it's more reliable than an interrogation”, “I think it's better than the diary they have to fill out. It's difficult.”). On the contrary, 6 HP expressed some reluctance to use it in specific conditions. They expressed concerns about the role of technology in a

human-to-human relationship that characterizes medical care (“The disadvantages...more ethically, it replaces the patient-doctor relationship. We say that we are going to do telemedicine and tell the patient ‘you no longer come for a consultation, you will send me your curves and I tell you how to adapt your treatments”). The number of references to “trust” in relation to “doubts” regarding the technology was equal. More importantly, the thoughts on BWS monitoring revealed questions about the functioning of devices (9 HP) and the need to help them use such a device in real-life (8 HP out of 9). HP required that particular attention had to be paid to their training (issues of how, when and for which patient BWS monitoring should be used, as well as how to apply the results) and to the logistical support (set up the monitoring and instruct the patients, give/return the device, get the results, *etc*). Finally, scientific proof of the usefulness to improve patients’ PD is needed. All HP suggested different ways to take advantage of motor symptoms measurement.

Suggestions for use

All HP expressed ideas for clinical care, and 5 HP also mentioned research purposes. The treatment adaptation was the main suggestion for using BWS in care. All HP considered BWS as a possible support tool to adjust oral medication, pump delivery, or deep brain stimulation, or to decide on the transition to advanced therapies. Three HP suggested that it could help minimizing or avoiding visits or hospitalizations. Another suggestion (3 HP) was to use BWS monitoring results for the therapeutic education of patients. Regarding research, HP thought the development of new targeted treatments would be eased by motor symptoms measurement, and they also suggested to focus on the study of other movement disorders. Further, 3 HP suggested the use of BWS monitoring to create an automatic system for real-time treatment adjustments according to motor symptoms measurement, and two contemplated direct feedback from the measure to an actuator, such as auditory cueing or fall alarms.

DISCUSSION

This study provided insights into the patients' and HPs' experiences of BWS. Both demonstrated a great interest in this new application, and both advantages and disadvantages of using the devices were proposed. To our knowledge, this is the first study that allowed confrontation of viewpoints of the two stakeholders on several PD specific devices.

Validated questionnaires revealed that the three BWS were acceptable (good usability assessed with the SUS) [36] and attractive (positive UX results with the AttrakDiff). Still, the ratings show there was room for improvement. Disparities were observed between the three patients' groups (especially regarding the disease duration and the gender ratio - Table 1), and the number of patients in each group was limited, but no correlation was found between the patients' characteristics and the questionnaires scores (Supplementary Table 2).

To summarize the participants' perception, and on the one hand, patients were enthusiastic and engaged in the experience because they hoped that a new tool could improve their PD management. The device use also raised expectations as the handling was largely felt simple and practical, and the device considered as an everyday life object. The patients expressed little worries about the potential constraints of their use and dissatisfaction, which did not have a strong effect on the general perception of BWS. Instead, the patients were curious and proposed improvements in device performance in terms of simplifying the manipulation (especially for patients living alone - Table 1) or using new materials. On the other hand, HP expressed some concerns about the implementation of BWS monitoring into their practice mainly because of the device logistics. Support from the expert staff was required, and time dedicated to training on the interpretation and reviewing the results was the limiting factor. However, they appreciated the accuracy and reliability that a continuous and objective ambulatory assessment of motor symptoms with high resolution could provide. HP also appreciated the ease with which the results could be read, as well as the ease with which patients could wear these devices.

The Movement Disorder Society (MDS) supports the implementation of BWS monitoring in clinical care and research [23]. This task force published a roadmap to facilitate monitoring

adoption, given the technology's maturity compared to the slow progression of its use in clinical care and research. Still, in this study, HP voiced fundamental requirements before complete adoption. Both patients and HP shared enthusiasm and suggested ways to use BWS monitoring in treatment adaptations or research advances. However, HP formulated the need for support measures for its implementation in practice that may not yet be totally deployed by healthcare organizations. HP also still needed an extended proof of the clinical relevance. Indeed, the technology readiness faces a lack of clinical evidence in its input for PD symptoms' improvement, which may impact the willingness of HP in using such systems. While Santiago et al. [49] demonstrated that physicians might already use the technology to facilitate treatment adaptation, the technology has not yet been adopted globally. Patients may be more willing to use BWS compared to HP. Patients indicated that they are ready to include BWS in their care pathway. This study is consistent with others that have shown very good acceptance of and readiness to wear quite complex systems [50,51]. According to Ozanne, "the benefits were valued higher than the possible inconvenience of wearing the sensors" (page 6) [52].

Thus, even though previous studies endorsed the use of BWS monitoring for PD in clinical practice and research [22], gaps in the application that restrain the full deployment have been identified. Healthcare organizations should develop a support system required by HP to follow MDS guidance and facilitate BWS monitoring while managing the barriers to BWS use [52]. This study offers strong support that BWS monitoring may be a support for clinicians in adjusting the treatment. Both patients and HP shared the idea that BWS monitoring could also facilitate discussion and benefit the interactions more than using the symptoms diary, as in Fisher's study [53]. BWS could help instruct patients about their symptoms and assist therapeutic education.

Moreover, patients might feel integrated into their care management when receiving feedback on their assessment with BWS [50], which would increase treatment adherence [54]. The active involvement of patients in their care through BWS monitoring might improve their situation and increase their quality of life and/or wellbeing [55]. Besides, this study showed that a few patients adapted their behavior without difficulty in order to improve the monitored

movements and then get encouraged by the results. The motivation generated by the possible consequences of BWS monitoring on health might encourage patients to pay close attention to their condition, so they adopt actions that may be more appropriate, which can be observed for fall prevention awareness, for example [56]. Further investigation should be done to explore whether BWS can generate a placebo effect that would enhance the patient's situation, as PD is known to be easily influenced by placebos [57]. That also gives rise to the need for controlled clinical studies when involving BWS monitoring. Furthermore, HP broached the opportunity to create automatic treatment delivery systems based on the results of the objective monitoring of BWS. Experts and manufacturers should explore the chances to set up such a system in compliance with the technical and the users' perspectives.

Methodological considerations

The strength of this study is that it considered the viewpoints of both patients and HP on three different BWS for PD before and after their use. The reliability of data is increased by the absence of inter-researcher bias, as only one researcher conducted the interviews, transcribed them, and analyzed the transcripts. Moreover, the external researcher who performed cross-checking of the codes agreed with the codes' categories and their description. During the second interview, patients confirmed the findings that emerged from the first interview, which decreased the conformity bias. On the one hand, a selection bias was one limitation since it was not possible to conduct the one-week experiment with the BWS b when patients could not guarantee internet connection. Maybe non-technophile patients would have expressed more negative feedback after complicated handling (number of techies in Table 1).

Moreover, the diversity of patients' profiles might have shaped their perception of the BWS tested. Additionally, the UX may have been affected by the seasonality effect, as all interviews of patients were performed during winter and fall. Some perceptions of BWS might have been different if the interviews took place during the summer months (for instance, greater visibility of the device to others, bands that keep warm and cause sweating). On the other hand, the phenomenological approach adapted from van Manen [58] is a well-established method for qualitative research and guarantees the trustworthiness [59] of this study's interpretation.

The findings that emerged from this study are hypothesis-generating rather than definitive; no consensus is aimed to be pronounced in this study. Perhaps, in a standard care context, those same patients would not have as many comments and suggestions of use. Therefore, the current study could be reproduced in other movement disorder centers to collect different viewpoints from various PD populations and help personalize BWS use to each one.

CONCLUSION

The study of the patients' and HP's perceptions of BWS monitoring seems to favor its use in research and care practice. The UX of patients was positive for the majority of patients, supporting the very good usability and the attractiveness of these study's devices. Patients and HP offered complementary opinions and suggestions for use. Both sides expressed their interest and enthusiasm in BWS monitoring. Few developments of new devices involving human-machine interaction consider the UX early in the process, but patients' and professionals' perceptions may help develop a system that will respond to the needs and the expectations of all stakeholders. Adhering to the recommendations of patients and professionals would maintain a final optimal use of BWS monitoring and its correct implementation to standards of care [60]. Although, clear clinical evidence of the relevance for PD care still remains necessary.

This study draws reliable information on the implementation of BWS in real-life situations in clinical practice and the real lives of PD patients. From those outcomes, healthcare organizations can carry out actions to answer the needs of patients and HP to organize an effective and efficient adoption of BWS monitoring. Manufacturers can also make the most of this experience to help organizations seek improvements in PD care through BWS monitoring.

ACKNOWLEDGMENTS

We greatly thank the patients and health professionals who participated in the study. We would like to thank Arlette Welaratne and Nathalie Lévêque for helping with patient recruitment and the Movement Disorder Unit from Pitié-Salpêtrière Hospital. We also are grateful to Léa Imbault

for helping with qualitative research methodology and to Gabriela Dye for proofreading the article.

CONFLICT OF INTEREST

CVF received a grant from Association Nationale de la Recherche et de la Technologie (A.N.R.T.) to conduct this project. CVF, YR and SH disclose full-time employment by Air Liquide Healthcare. CH declares no conflict of interest. JCC served on advisory boards for Air Liquide, Biogen, BrainEver, Denali, EverPharma, Prevail Therapeutic, UCB, and received grants from Sanofi outside of this work. DG received received research funding from Air Liquide HealthCare; received grants from AP-HP (DRC-PHRC) and France Parkinson, served on scientific advisory boards for AbbVie and Zambon; received speech honorarium from Medtronic, Abbvie and Merz; received travel funding from Abbvie and Merz.

SUPPLEMENTARY MATERIAL

Supplementary data and figures are:

- selected quotations from the interviews of patients (Supplementary Table 1);
- correlation coefficients and p-values between the questionnaires scores and the age and disease duration (Supplementary Table 2).

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FIGURES AND TABLES

Figure 1: Participation protocol for patients and health professionals

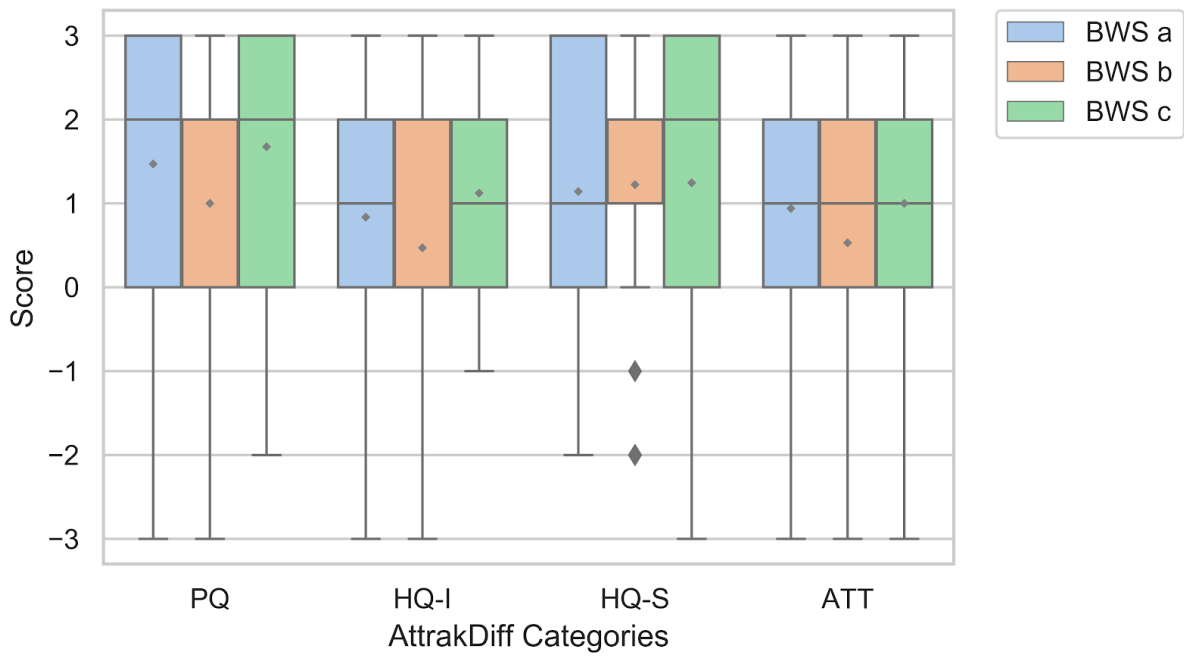
Patients			
1st Interview Phenomenological Approach	Experience with the BWS	2nd Interview Phenomenological Approach	SUS and AttrakDiff Questionnaires Semi-quantitative Approach
60 - 90 minutes	1 week	30 - 60 minutes	
Health Professionals			
Interview (20 - 60 minutes) Phenomenological Approach			

Table 1: Patients' characteristics in each group.

Group	BWS a (n = 7)	BWS b (n= 8)	BWS c (n = 7)	All (n = 22)
Gender ratio (male/female)	2/5	6/2	1/6	9/13
Age (years) median [range]	71 [63; 79]	59 [41; 71]	68 [64; 75]	65,5 [41; 79]
Disease duration (years) median [range]	1 [1; 17]	8,5 [2; 17]	10 [1.5; 14]	7,5 [1; 17]
Number of techies*	5	7	5	17
Living alone	0	2	0	2
Previous knowledge of BWS	0	2	0	2

Techies and non-techies were defined from the patients' self-description of usual technology mastery (smartphone, computer, *etc*).

Figure 2: Results of the AttrakDiff questionnaire.



Boxplot for each BWS rated with pragmatic qualities (PQ), hedonic qualities linked to the user (identification of the user to the product: HQ-I), hedonic qualities linked to the product (stimulation generated by the product: HQ-S) and attractiveness (ATT).

Table 2: Themes broached across time.

	First Interview		Second Interview
	Before discovery	After discovery	After use
Positive	<p>CURIOSITY ENTHUSIASM "NO PROBLEM" EXPECTATIONS HOPES INTEREST</p>	<p>CURIOSITY HOPES ENTHUSIASM EXPECTATIONS INTEREST "NO PROBLEM"</p>	<p>CURIOSITY HOPES EXPECTATIONS ENTHUSIASM GOOD FEEDBACK INTEREST "NO PROBLEM"</p>
Negative	<p>CONSTRAINTS APPREHENSION DOUBTS NEGATIVE A PRIORI</p>	<p>DISAPPOINTMENT SOCIAL DIFFICULTY DOUBTS APPREHENSION CONSTRAINTS NEGATIVE A PRIORI</p>	<p>DISAPPOINTMENT APPREHENSION HELP NEEDED CONSTRAINTS DOUBTS INCONVENIENCE / BUG SOCIAL DIFFICULTY</p>

Characters' sizes reflect the number of patients who expressed those themes during the interviews.

SUPPLEMENTARY DATA

Supplementary Table 1: Quotations from interviews, which illustrate the general perception of BWS of patients.

	Before use	After use
Hopes	<p>01UR: "maybe it's going to come out of extraordinary stuff"</p> <p>06UR: "It's curiosity [...] we want to understand"</p> <p>12UR: "It's great because I never know where to put it on the sheets. It's always very complicated, it's better if there is a device that records them. It's an advantage. It will replace the sheet which is very difficult to fill"</p> <p>15UR: "I think it can be an aid with several drawers. I feel like it can be useful to patients and doctors, and to any team around the patient"</p> <p>30UR: "an impression like that, I say to myself: "finally", this is my point of view, I say finally because from the start I have no reference bar"</p>	<p>01UR: "Anything that can improve my life, I'm up for it"</p> <p>08UR: "it would be an assistance, a more precise additional measure"</p> <p>11UR: "I see as a useful aid to doctors in relation to the objective sign which is interesting, in relation to what the patients can bring back from their experiences which are subjective and possibly more romanticized...which doesn't have the rigor of a recording like that"</p> <p>12UR: "It helps the patients to tell, it helps the relationship between the patients and the neurologists. To put it exactly like that, it's that neurologists can tailor treatments to the things that happen, to the lives of the patients"</p>
Expectations	<p>09UR: "So it will be much more precise and useful than if I wrote down the moments of difficulty hour by hour. It will be more precise and more reliable"</p> <p>14UR: "I manage to describe how I feel in consultation a little bit but not so much, we are always a little bit...vague. I could surely say more things during the consultation"</p> <p>30UR: "It would first be useful for the practitioner because when he asks us questions, we have answers...well, I'm too neutral in my dialogues, I don't know how to describe in fine detail if things are better, if it doesn't get better at such a time of the day, 6 months later. I can't say if it gets better than such 6 months before, at some other time of the day, it's subjective."</p>	<p>09UR: "I give a vague answer but it is not objective. While with these measures, we can see an objective basis to inform the doctor"</p> <p>11UR: "In my idea it was a device that was going to be more than a clinician"</p> <p>14UR: "actually trying to see, trying to clarify a little, the why of these movements, these tremors which are sometimes increased and sometimes not. Why are there days when everything is going well and days when it is not going well because it is true that indeed we do not always see causes"</p> <p>30UR: "Finally we are going to measure something at home because for 7 years, nobody has measured anything at all, I do not know where I am compared to what I was and finally something concrete"</p>
Fears	<p>01UR: "in front of people it's complicated"</p> <p>10UR: "I was a bit scared, I thought I was going to carry a lot of things on me"</p> <p>14UR: "I am not saying that it is not good but I think that one should not make a blind confidence. We must also analyze what we feel what we see. You can't just rely on the device"</p> <p>27UR: "Sometimes there are things we can have that we prefer not to know"</p>	<p>01UR: "Can we check if it worked well? It's the fear of not using it well"</p> <p>03UR: "On the other hand, there was a moment when I was afraid that it would go away because of my dyskinesias. It can't go, does it hold up well?"</p> <p>04UR: "I felt a little spied on"</p> <p>06UR: "it is an apprehension compared to the evaluation of the stage of my disease"</p> <p>31UR: "there are people who will not be able to bear to see evolution"</p>
Questions	<p>02UR: "Can we visualize the results? How is it transcribed to you?"</p> <p>15UR: "Do you compare the results of different patients with each other too? Will having this device on me make me more vigilant for example?"</p> <p>29UR: how do you know it's related to the disease or not?"</p>	<p>06UR: "I was curious, I said to myself but what does it record in fact? Is it the movement of the wrist, is it the whole shoulder... Is it the rhythm... I wondered what evaluations it gave"</p> <p>09UR: "Can we make the recordings speak? Can we watch a recording to understand what it is?"</p>

Quotations were translated from French, the interpretation sense may slightly differ from one language to another.

Supplementary Table 2: Association study between the questionnaires scores and patients' characteristics

	SUS		AttrakDiff total score		ATT		PQ		HQ-I		HQ-S	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age	0.18	0.44	-0.03	0.89	-0.07	0.75	0.12	0.60	0.16	0.50	-0.21	0.35
Disease Duration	-0.09	0.70	-0.08	0.72	-0.289	0.20	0.03	0.91	0.10	0.65	-0.09	0.69

Pearson correlation coefficients (*r*) with p-values (*p*).

3.2 Theoretical framework of presented results

In this study, we used three approaches to obtain a general point of view on BWS perception among patients and HP: a usability and user experience study via questionnaires, and a phenomenological analysis through interviews. We present additional information related to these approaches. The two questionnaires are available in Supplementary Material III. The interview guides used for patients and HP (in English) are also part of the Supplementary Material IV.

3.2.1 Questionnaires for usability and user experience assessment

Usability is the aptitude for use, which we evaluated in this study with the System Usability Scale (SUS) that is presented in the Supplementary Material III (Bangor, Kortum, and Miller 2008). It evaluates a situation of use of a tool by a user (expert or not) to successfully achieve specific objectives. In this study, the success achieved by patients with a BWS is adherence to wearing the device to collect exploitable data. The expected success when a HP use BWS is the provision of relevant information to support their practice in PD management. Usability has to be distinguished from utility, which represents the suitability of the tool with the activity. Usability is described by three criteria: effectiveness, efficiency and satisfaction, which are defined by an ISO standard (9241-11 (“ISO 9241-11” 2018)). User experience (UX) goes beyond this first notion to add the idea of how each user feels, thus encompassing functional and non-functional qualities (*e.g.*, aesthetics). UX has been controversially defined as the “perceptions and reactions of a person that result from the actual and/or anticipated use of a product, system or service” (ISO 9241-210 (“ISO 9241-210” 2019)). Two approaches have emerged following this disagreement between authors: holistic approach and multidimensional approach. The first is based on a phenomenological aspect of the experience by offering a

unique feeling of the experience while the second, although not completely opposed, assesses different dimensions perceived by individuals. UX often categorizes the quality of a product into its pragmatic (instrumental) and hedonic (non-functional) qualities, which are assessed with the AttrakDiff used in our study and presented in the Supplementary Material III (Lallemand et al. 2015). Few studies combine multidimensional descriptions of the UX and acceptability theories to assess the perspectives of patients in the use of BWS.

3.2.2 Interviews

For both patients and health professionals, semi-structured interviews were conducted according to a certain methodology.

A phenomenological descriptive approach (Husserl 1970) was followed in order to understand the events experienced by users from their subjective narrative (Ribau et al. 2005). Phenomenology is a scientific approach for lived experiences, which allows the identification of themes that characterize the perception of the lived experience seized during the interview. The exchanges during face-to-face discussions reveal facts, needs and stories of concrete experiences. They allow the exposition of what is positive and negative in the UX. The qualitative analysis of feedback allows for a consideration of the emotional component when using a device. The emotional sphere plays a role in attitude and the performance of tasks during device use (Pessoa 2008). Moreover, emotions are also known to influence PD symptoms, and conversely (Berlot et al. 2020). A tool such as BWS evokes emotions that may stimulate different behaviors according to their positive or negative valence (Agarwal and Meyer 2009). These behaviors are thus influential in the success of the interaction between the tool and the user, and in the user experience.

In order to answer our questions, the interviews were designed using the explanatory interview technique (Vermersch 1994). The interview, based on a guide, was semi-structured with open

questions. This type of interview is the ideal way to facilitate free expression while also maintaining the direction of the subject. Thanks to open-ended semi-directive questions, the explanatory interview allows for the gathering of a description of the overall lived experience and a more precise understanding of the actions carried out for manipulation of the system in the context of use. The phenomena of interest are considered from the user's point of view and the questions are guided so that the interviewee becomes aware of the action that may have been carried out automatically and/or unconsciously. The conceptualization of actions is not obvious and this technique aims to seek the verbalization of tasks performed by the user.

The information gathered during the interviews is qualitative data that must be reduced, summarized and transformed in order to be able to group and compare the data. Thus, it is necessary to go through three stages before the phenomenological analysis: taking notes during the interview, transcribing the interviews, and coding these transcripts.

In our study, the methodological approach was inspired from qualitative studies in the experience of patients living with chronic conditions. The coding of the transcripts was performed with qualitative software to create a structured analysis (Lawson et al. 2018; Bogner et al. 2017). First, we created codes that correspond to defined meaning units transmitted by each sentence or group of words (Meis et al. 2014; Charlton and Barrow 2002; Read et al. 2019). This first step may be considered as a naïve understanding (Lindgren, Storli, and Wiklund-Gustin 2014). Then, the meaning units were gathered into main themes, which were classified into categories and subcategories with hierarchical relationships (Genoe and Zimmer 2017; Jonasson et al. 2018). This second step may correspond to the structural analysis of the codes, which provide an explanation of the ideas expressed. And finally, the comprehensive understanding involved back and forth between the transcripts and the themes broached to confront the interpretations of the text. Then, the findings were linked to the questions asked in

this study, and a global interpretation of the BWS perception by all patients or HP could be elaborated according to the importance granted to each theme.

3.3 Backing of presented results

Other comments reported by patients during the interviews were not described in the qualitative study (Virbel-Fleischman, Rétory, et al. 2020), although some of them are depicted here.

For a majority of patients, the primary interest in participating in this study was to make research progress. BWS monitoring was a completely new word for many of them, but finding a new avenue to help patients with PD was the driving force behind volunteering. The progress inspired by this new term was perceived as positive and the objectives attractive (*"It is very serious to carry out this type of investigation"*). Technology seemed to be an attractive path to *"make a difference"* in the field of PD. We may forecast that patients would be even more enthusiastic about the idea to improve their PD care management with an intelligent system capable of automatic treatment adaptations. Curiosity was a predominant attitude when the patients were included in the study. Few were informed about BWS monitoring and patients developed an imagination around BWS and many questions emerged from these personal reflections: *"What does it look like?"*, *"What will it measure?"*, *"Must we wear it all the time, even while sleeping?"*, *"How does it measure?"*, *"What do we get in relation to the disease?"*. Once the device was discovered, the questions became more precise regarding the functioning of the technology for certain patients with a technophile profile, and on the rules of use. Some patients compared the device to apomorphine pumps (*"It doesn't seem big compared to the pump"*) or to a cardiac Holter (*"I see the same principle as a Holter, it does the same thing, but it seems less restrictive"*). All patients expressed the possibility of adapting their therapy based on the objective measurement of their symptoms. This statement is in favor of the

implementation of new technical approaches for the follow-up of PD patients, which is similar to other pathologies.

The physical characteristics of the three BWS were trivialized (*“aesthetically simple”*) while the usefulness of the tools was questioned (*“I find it more useful for a researcher than for me”*, *“I need more explanations and to see what it gives as results”*), or, on the contrary, it was supported (*“I think that it could replace the diaries which are complicated to fill, I could show that to the doctor instead of the sheets”*, *“It would be an aid for the management of everyday activities”*). According to the instructions given during the presentation of the device, patients sometimes anticipated that they might forget to do the necessary manipulations during the week of use at home, which created some concerns (*“fear of doing it wrong”*). The constraints that were felt prior to use were minor for all patients. However, a more complex system such as the closed-loop system might engender more apprehension. Anxiety might arise from the risk of malfunction of a hypothetical adaptive CSAI with incorrect delivery of apomorphine. Indeed, this system would involve several devices and require elaborate functions that must work in harmony to trigger a direct impact on the patient.

In addition to a well-thought user interface, patients, and HP too, may need support in the management of such a system at home to feel confident about the results and assurance on how to avoid errors (Schnittker 2016; Fairbanks 2004). The desire to gather useful information for PD was greater than the embarrassment imagined compared to what inconveniences from wearing of the device would potentially cause for a week (*“If it helps, then we don't care that it could interfere”*). And finally, the device instructions supplied for the week of use were sufficient for adequate handling at home. The development of a closed-loop system might target limited interactions between the various components and the user to lessen the demand in terms of instructions necessary to understand and recall in the long-term.

In most cases, the use over one week was “normal”, “trouble free”, “without any issue”, the device was “simple”, “easy”, etc. The general feedback was positive (“It was a normal week”, “I forgot I had it”, “Everything was fine”). Only a few specific and individual situations should be noted.

Eight patients expressed the feeling of being observed, monitored or even spied on: “We ask ourselves the question, it is a bit embarrassing, then we move on and we keep on wearing it, then we forget”, “I removed it to go to the toilet even if I suspected that it was not important for you”, “In a way, it is an intrusion in our lives”. BWS might be the object of persecution delirium in patients treated by dopamine agonists who developed delusions and hallucinations (Warren et al. 2018). Importantly, closed-loop systems must offer secured connected devices to protect health data and manufacturers may be able to reassure patients on the process of having their personal data stored online.

Two patients changed their behavior thinking that their movements were recorded. These changes in attitude should not change the results of monitoring and were not disturbing for patients who decided to act differently in order to produce a more complete or longer movement recordings. This attitude might reveal a possible “placebo” effect, which has been recognized in PD patients, and that should be further investigated in the case of BWS (de la Fuente-Fernandez 2001). According to another patient, the device was “Disruptive in itself, we carry something new with us, we are careful about what we do to perhaps avoid manipulation, and have it all the time, and we get organized according to it”. Some patients have expressed mild device-related discomfort, but this did not engender the patients to stop wearing the device as a solution was often found quickly (“It is sometimes uncomfortable if you think about it, but it is not unbearable”). The position of the device on the body may directly impact comfort when movements are performed or while still in a specific position. The design of devices should not interfere in the normal actions of patients nor engender an additional burden to life with the

disease (Bruno et al. 2020; Simblett et al. 2020). Also, the tolerance assessment of BWS in this study was obtained from a one-week experience. The duration of use might impact the tendency to tolerate different levels of discomfort or *ad-hoc* inconvenience, while closed-loop systems may not be only temporary in a patient's life. Thus, careful attention should be paid to insure long-term comfort for patients living with medical devices.

Device aesthetics was not a major issue, but it was noticed by all the patients who did not find the devices physically attractive. Patients also noticed that an embarrassing situation would have appeared in the summer, with light clothes showing the wrists or ankles (all patients experienced the week of use in relatively cold weather conditions). Some patients even said that their opinion would have been completely different because activities at the water's edge and clothing habits would not have been compatible with the device. Moreover, when addressing the question of the device's visibility to others, points of view split into indifference or possible embarrassment. Nine patients expressed the wish to not have the device visible.

Apart from device outlook and usability and convenience to patients, a HP may first require from a BWS that it report true insights of the patient's condition and that interpretation be accessible, to complement already existing information in the most effective manner. A dedicated protocol for presentation and education of patients to BWS should be implemented to maximize the chance for correct use and understanding of the objectives to target optimal compliance. In CSAI therapy, education on the therapy and training are indicated for essential success in treatment, including motivation of the patient, family and caregivers (Trenkwalder et al. 2015). Contextual information is also key for acceptance of the device (Wu and Munteanu 2018). Thus, apart from the tool tolerability by patients and HP, the approach behind BWS must be understood and approved. Finally, the objectives of a hypothetical closed-loop system in PD should be clear for patients and HP in order to gain adherence.

3.4 Users are BWS-ready, but how would health professionals take advantage of it to treat patients?

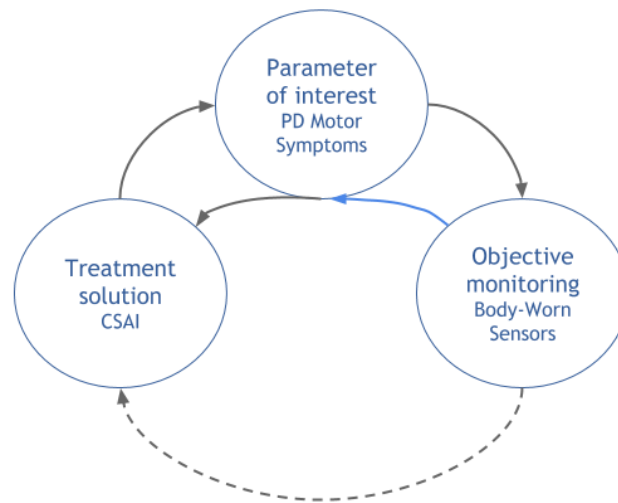


Figure 18: Scheme of adaptive CSAI based on BWS monitoring of motor symptoms in line with a closed-loop system. Dashed lines are links uncovered by the literature. The blue line represents the link we have studied in this section of the manuscript. The opposite sense was described earlier in the manuscript

The outcomes of this study facilitates discussion about possible protocols of use for BWS according to monitoring objectives decided by the HP and the patient's profile, as well as requirements to include BWS monitoring in PD management in appropriate conditions. Moreover, the results regarding usability and acceptability of patients support the possibility of a new paradigm in PD follow-up. Patients may demand new tools to better treat their symptoms, to empower in their own disease management, and a HP may consider using validated new technologies to support their practice. Thus, the link between the parameter of interest and the BWS may be feasible and well-engaged for a hypothetical closed-loop system (Figure 18). However, significant responsibility lies in the correct reading of monitored results to adapt therapy, and how information that is collected from BWS is interpreted into treatment decisions is still unsettled. This will be the subject of the next study.

4. A new approach regarding BWS effect on therapeutic decisions

Previously, we showed the possibility for a new paradigm in follow-up of patients with CSAI therapy through the use of BWS. We also presented qualitative results in favor of the implementation of BWS in real-life practice, from both patients and PD specialists. Nonetheless, to date, the objective monitoring of motor symptoms is still not a part of the PD standards of care. However, BWS in clinical practice may change the standards of care. Indeed, the relevant data from BWS results is different from the usual collected information in standard practice. To date, there is no correspondence to decode its connection with decisions in treatment. Thus, this new type of information may require new guidelines to support neurologists in decision making on therapeutic actions. Currently, many crucial aspects of this decision are unknown while the selection of criteria from objective monitoring results may determine the precision of treatment adjustment, especially in a closed-loop system. The influence of definite BWS outcomes may vary according to their type, and they may trigger unique therapeutic actions which should be precisely explicit. Therefore, we intended to study the target elements of a type of BWS report used by neurologists to act on treatment of PD patients.

4.1 Motor symptoms assessment and treatment adaptation in Parkinson's disease based on body-worn sensor report: what is the agreement among neurologists? [Submitted] (Virbel-Fleischman, Mousin, et al. 2020)

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Keywords

Parkinson's disease - Body-worn sensors - Treatment adaptation – Agreement

Highlights

- Objective monitoring may help professionals in making decision for treatments
- Sensor-based symptom detection in PD is consistent among neurologists
- Treatment adaptation based on sensor reports is consistent among neurologists
- Summarized symptom scores from sensor predict treatment adaptation

Declaration of interest

CVF received a grant from Association Nationale de la Recherche et de la Technologie (A.N.R.T.) and full-time employment by Air Liquide Healthcare.

FM, YR, SL and SH declared full-time employment by Air Liquide Healthcare at the time of the study.

JCC served on advisory boards for Air Liquide, Biogen, BrainEver, Denali, EverPharma, Prevail Therapeutic, UCB, and received grants from Sanofi outside of this work.

IB served on scientific advisory boards for AbbVie and Orkyn.

DB received travel grants from Boston Scientific and research support grant from Fondation Recherche Médicale.

MB reports reimbursement of travel expenses to scientific meetings from ELIVIE, Medtronic and Boston Scientific, honoraria from Merz Pharma and Allergan for lecturing, outside the submitted work.

VCDC and SF declare no conflict of interest.

SD declares boards and congress with Medtronic, Orkyn, AbbVie, LVL, Homeperf, Elivie.

CG received grants from Abbot and Abbvie.

DD served on several Scientific Advisory Boards for Orkyn, Air Liquide, Lundbeck, Ever Pharma and Boston Scientific, he has equity stake in InBrain Pharma.

DG received grants from AP-HP (DRC-PHRC) and France Parkinson, served on scientific advisory boards for AbbVie and Zambon; received research funding from Air Liquide; received speech honorarium from Medtronic, Abbvie and Merz; received travel funding from Abbvie and Merz.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data,

(2) drafting the article or revising it critically for important intellectual content,

(3) final approval of the version to be submitted

CVF: 1, 2, 3

FM: 1, 3

SL: 1, 3

SH: 1, 3

IB: 1, 3

DB: 1, 3

MB: 1, 3

VCDC: 1, 3

SD: 1, 3

SF: 1, 3

CG: 1, 3

JCC: 1, 3

DD: 1, 3

YR: 1, 2, 3

DG: 1, 2, 3

ABSTRACT

Introduction: Treatment adjustments in Parkinson's disease are challenging due to symptom fluctuations and pitfalls in clinical data collection. Body-worn sensors could provide valuable information to support neurologists in implementing therapeutic actions based on objective monitoring, which may be considered as a tool to assist in a medical prescription. The translation of gathered data into relevant information for treatment adaptation remains pivotal. This study aimed to describe practices related to antiparkinsonian treatment adaptations as determined by a panel of neurologists analyzing anonymous patient profiles according to objective monitoring of motor symptoms.

Methods: The clinical profiles of eight patients and their monitoring results were blinded and presented to eight neurologists with a questionnaire regarding interpretation. We collected the answers and subsequent therapeutic decisions. Any relationship between interrater agreements in the PKG reading and the severity of symptoms were analyzed via correlation studies. A logistic regression was done to observe possible associations between the PKG reports and the suggested treatment modifications.

Results: The interrater agreements in symptoms' assessment were significantly associated with various PKG scores (for instance the median scores of bradykinesia and dyskinesia: $r=-0.74\pm 0.01$ and $p<0.05$). The summarized PKG scores influenced the treatment modifications (for instance, the highest percent time immobile favored a treatment increase: mean 0.9).

Conclusion: Our results suggested relevant monitoring information to investigate while looking for treatment adaptations. A loop system may be hypothesized to directly and automatically suggest treatment modification from this information, which supports progress in the development of practices to improve patient care with sophisticated tools.

LIST OF ABBREVIATIONS

BKmed: Median of the continuous bradykinesia score

BK75: Third quartile of the continuous bradykinesia score

BK I: Percent of time with bradykinesia at severity level I per periods of 3 hours

BK III+IV: Percent of time with bradykinesia at severity level III+IV per periods of 3 hours

BK Q1: Global first quartile of the bradykinesia score

BK Q2: Global second quartile of the bradykinesia score

BK Q3: Global third quartile of the bradykinesia score

BKS: Bradykinesia Score

BWS: Body-Worn Sensor

CSAI: continuous Subcutaneous Apomorphine Infusion

DAT: Device-Aided Treatment

DKmed: Median of the continuous dyskinesia score

DK75: Third quartile of the continuous bradykinesia score

DK I: Percent of time with dyskinesia at severity level I per periods of 3 hours

DK III+IV: Percent of time with dyskinesia at severity level III+IV per periods of 3 hours

DK Q1: Global first quartile of the dyskinesia score

DK Q2: Global second quartile of the dyskinesia score

DK Q3: Global third quartile of the dyskinesia score

DKS: Dyskinesia Score

FDS: Fluctuation Dyskinesia Score

LEDD: Levodopa Equivalent Daily Doses

PD: Parkinson's disease

PTI: Percent of Time Immobile

PTT: Percent of Time with Tremor

INTRODUCTION

Treatment of Parkinson's disease (PD) is based on dopaminergic substitution pharmacotherapy. The response to dopaminergic drugs evolves throughout the disease course. After seven to ten years from onset, fluctuations and dyskinesia eventually occur [\(1\)](#).

At this stage, patients may require device-aided therapy (DAT) to overcome the challenges of treatment optimization. All DAT, including deep brain stimulation, continuous subcutaneous

apomorphine infusion (CSAI) or levodopa-carbidopa intestinal gel are efficient in reducing fluctuations and improving quality of life [\(2–4\)](#). However, making the right decision regarding DAT initiation or follow-up may be difficult, partly because collecting information about symptoms and their daily variations is challenging [\(5\)](#). Objective measurement of movements may increase the level of accuracy in symptom evaluation and better guide therapeutic decisions [\(6\)](#). Body-Worn Sensors (BWS) are devices that continuously monitor activity during daily-life without medical supervision, and translate motor parameters into normal movement, akinesia, dyskinesia or tremor. BWS monitoring use is spreading [\(7,8\)](#) and expert panels have investigated usage to provide guidance for application in clinical practice [\(9\)](#).

The PKG System (Global Kinetics Corporation ®, Australia) is a wrist-worn device that automatically quantifies bradykinesia, dyskinesia and tremor. The PKG algorithm has been validated against gold-standards: experts [\(10,11\)](#), video [\(12\)](#), patient diaries [\(13\)](#), and clinical rating scales [\(14\)](#). There is emerging evidence suggesting that it could be a valuable tool for therapeutic management [\(7,9,15–17\)](#). However, this requires further confirmation. Importantly, how information from a BWS, including PKG, is translated into symptoms by clinicians in order to identify relevant targets for treatment adaptation is still a black box. Thus, our aim was to i) highlight the relevant outcomes of PKG and reveal if this information is consistently identified by the clinicians, ii) examine therapeutic decisions based on this information, and iii) investigate the link between outcomes and decisions.

METHODS

We conducted an observational study among neurologists that were asked to analyze the results of PD patient monitoring. At the time of the study (August 2019 - February 2020), participants were investigators of a randomized controlled trial (@ctipark, NCT03213379) from which patients' data was collected and used as part of this study. A local ethics committee approved the study (CPP Nord Ouest IV).

Procedure

Eight neurologists (raters) considered as movement disorder specialists volunteered to participate in this study. They all practiced in Parkinson specialty centers with 3 to 20 years (median 13 years) of experience in neurology. They were trained for PKG reading and interpretation as part of the @ctipark study. They analyzed 9 [2, 50] PKG readings before their participation (median [minimum, maximum]). For all cases submitted to the raters, the patients were treated with conventional medication and CSAI. Additional information is described in Supplementary Table 1. Selected information from eight random patients constituted the eight cases (Supplementary Figure 1):

- PKG report automatically generated by the proprietary algorithm;
- Antiparkinsonian treatments and therapies for major comorbidities, if present;
- Context (age, gender, weight, height, duration of PD since diagnosis, duration of dyskinesia since appearance, scores of the Movement Disorder Society - Unified Parkinson's Disease Rating Scale and Montreal Cognitive Assessment scale when available)

We used an identical number of raters and subjects to minimize variance in interrater reliability (18). All eight raters studied all eight cases resulting in 64 unique combinations to study.

Data collection

The PKG Watch was worn over seven days for real-life monitoring at each patient's home. The monitoring results (PKG) showed the progression of bradykinesia (BKS) and dyskinesia (DKS) during the daytime (5 A.M. - 10 P.M.) at four levels of severity (I, II, III and IV). BKS and DKS were produced every two minutes and displayed in the main PKG graph as the median and the first and third quartiles of severity scores, for all days monitored and according to time. A second graph showed the percent of time spent in severity levels I and III+IV, per interval of 3 hours from 6 A.M. to 9 P.M. The PKG also displayed graphs for the occurrence of tremor, immobility periods and a summary of scores.

The eight raters received a two-part questionnaire with each patient's case to report their evaluation and suggest treatment adaptations (Supplementary Figure 2).

The first part applied to the PKG reading by raters. They had to signal if the symptom (bradykinesia, dyskinesia, and tremor) was significant, and to specify the number of occurrences per day they observed and the duration of each period.

The second part of the questionnaire was related to treatment adaptation suggestions for conventional treatment (total dose, number of intakes) and CSAI therapy (duration of apomorphine delivery and flow rates).

Integrated information directly provided by the PKG and reflecting the severity of symptoms with various time scales were collected:

- Percentages of time at severity levels I and III+IV, per periods of 3 hours (BK I, BK III+IV, DK I, DK III+IV);
- The global first (Q1), second (Q2) and third (Q3) quartiles of the BKS and DKS (BK Q1, BK Q2, BK Q3, DK Q1, DK Q2, DK Q3);
- Summarized Fluctuation Dyskinesia Score (FDS);
- Summarized Percent of Time Immobile (PTI);
- Summarized Percent of Time with Tremor (PTT).

Other continuous parameters from the PKG were obtained via standardized methods:

- Continuous BKS and DKS medians and third quartiles (BKmed, BK75, DKmed, DK75, respectively): severity level interpreted by 30-minute periods by visual interpretation of the main graph from 5 A.M. to 10 P.M. From each time period, the score (I to IV) was determined from the severity level that occupied the most time.
- Continuous percent of time with tremor (Tremor Score): hourly score obtained from an image analysis of the tremor graph. Each hour was extracted separately via a transitional disclosure of the color intensity of the global frame and the representation of tremor episodes in dots. The Tremor Score was calculated using the space filled by dots per hour over the 7-day monitoring period.

From these continuous scores, coefficients of variation were computed per patient case, with the score means and standard deviations obtained by a 30-minute period to obtain intra-case variability.

Data analysis

The raters' answers were gathered by patient case. The number of raters detecting a symptom at each 30-minute period was computed for bradykinesia, dyskinesia and tremor from 5 A.M. to 10 P.M. The agreement between raters for each period in the assessments of bradykinesia, dyskinesia and tremor were independently computed by taking into account detections and non-detections of each symptom (range [50; 100]%).

Conventional and apomorphine Levodopa Equivalent Daily Doses (LEDD) were computed following Tomlinson et al. (19) to obtain total LEDD (sum of the two). We studied the difference between the initial and the suggested total LEDD by each rater, and the agreement between raters about the direction of the total LEDD modification (increase, decrease or stability; range [50; 100]%).

A correlation study was performed between the interrater agreements and the integrated PKG parameters using Pearson's method (normality validated with the Shapiro-Wilk test). Spearman's correlation method was used to study the relationship between the interrater agreements and the continuous PKG parameters.

We performed a 3-class-one-versus-all logistic regression after bootstrapping the 64 combinations (8 cases and 8 raters) to describe and estimate the impact of the patient's case *per se* (case variable), the rater, the patient's age, the integrated PKG scores summarized as FDS, PTI and PTT, on the direction of the total LEDD modification. Because amantadine could be added in order to reduce dyskinesia, a LEDD increase only due to amantadine adjunction was classified as equivalent to a treatment decrease (20).

We used Python Software Foundation to perform the analysis (Python Language Reference, version 3.7.4 Available at <http://www.python.org>).

RESULTS

PKG reading

The interrater agreements in the evaluation of bradykinesia, dyskinesia and tremor for all cases was high (median in % [range in %]: 89 [72, 100], 93 [71, 100] and 99 [89, 100], respectively) (Supplementary Table 2).

The association between interrater agreements in the symptom assessments and the severity of bradykinesia and dyskinesia PKG scores expressed at different timescales is described in Figure 1, A and B. The agreement in bradykinesia assessment was negatively correlated with the integrated PKG scores reflecting bradykinesia's highest severities (BK Q2: $r=-0.73$, $p=0.04$, and BK Q3: $r=-0.76$, $p=0.03$; $n=8$). There was no correlation with either BK Q1 or PTI.

The agreement in bradykinesia assessment was negatively associated with the continuous measures of bradykinesia (BKmed: $r=-0.58$ $p<0.0001$, and BK75: $r=-0.54$, $p<0.0001$; $n=272$).

The agreement in dyskinesia assessment was negatively correlated with the integrated PKG scores reflecting dyskinesia's highest severities (DK Q2: $r=-0.75$, $p=0.03$, and DK Q3: $r=-0.95$, $p=0.0003$; $n=8$). There was no correlation with DK Q1. In addition, the interrater agreement in dyskinesia assessment was negatively correlated with the continuous measures of dyskinesia (DKmed: $r=-0.63$, $p<0.001$, and DK75: $r=-0.60$, $p<0.0001$; $n=272$), and with FDS ($r=-0.90$, $p=0.003$; $n=8$).

The interrater agreements were also significantly associated ($p<0.0001$) with the percentages of time spent in severity levels I and III+IV by intervals of three hours ($n=40$, Figure 1). For bradykinesia and dyskinesia, the association was positive for the lowest severity level ($r=0.74$ and $r=0.69$, respectively), while it was negative for the highest severity level ($r=-0.79$ and $r=-0.80$, respectively).

Interrater agreement was also studied in line with variations in symptoms across the monitoring period. Interrater agreements for bradykinesia and dyskinesia were not correlated with the coefficients of variation of the continuous bradykinesia scores (BKmed nor BK75) and of the continuous dyskinesia scores (DKmed nor DK75), respectively.

Moreover, correlation studies showed that interrater agreement in tremor assessment was negatively associated with the Tremor Score ($r=-0.50$, $p<0.0001$, $n=136$; Figure 2), and with PTT ($r=-0.94$, $p<0.001$; $n=8$). Finally, there was no relationship between the agreement for tremor and the intra-case variability of the Tremor Score.

Treatment adjustments

The raters suggested modifications of the initial treatments for all patients such that the total LEDD could change and be different for the same patient case. The total LEDD suggested by the adaptations ranged from 60% to 305% of the initial treatments (Figure 3). Total LEDD augmentations suggested in Cases n°2, n°3 and n°6 by Rater 1, Rater 5, and Rater 3, respectively, were exclusively due to amantadine addition in order to reduce dyskinesia and could thus be considered in agreement with dose reduction for other dopaminergic medications. The agreement in treatment direction was globally high (median in % [range in %]: 81 [50, 100]; Supplementary Table 2), but varied among the cases. The raters unanimously agreed for two cases (n°5 and n°7) and disagreed at 50% for one (n°8).

Link between the case analysis and treatment adjustments

Finally, we tried to better understand the relationship between the treatment modifications and information from the patients and their PKG. We could not establish any significant correlation between the agreement in treatment modification and the agreement in the assessment of the three symptoms.

Thus, we studied independently the 29 suggestions of total LEDD increase, the eight suggestions for stabilization and the 27 decrease suggestions. The resulting model had good accuracy (classification rate of 86%).

Whatever the case, the eight raters had different tendencies in suggesting treatment modifications. The case variable had an impact on the treatment modification direction, independently from age, initial total LEDD and FDS, PTT and PTI (Supplementary Table 3).

From a clinical point of view, age, initial total LEDD, FDS, PTI and PTT could predict the LEDD change. The lowest initial total LEDD favored an increase of the total LEDD. The highest PTI and PTT scores favored an increase of total LEDD while the highest FDS were in favor of its

decrease (Table 1). Reciprocally, the opposite values favored the reverse action. In comparison to the other parameters, age had no or less impact (coefficient's absolute mean value below 0.3, Table 1).

DISCUSSION

Although not unanimous, the PKG reading for the assessment of bradykinesia, dyskinesia and tremor, and the directions of treatment adaptations were consistent among neurologists. Scores that summarize these symptoms in the PKG could influence the decision: the highest FDS scores favored a total LEDD decrease, and the highest scores of PTT and PTI favored its increase.

The variability in scores describing the symptoms could be a reason for the discrepancy between neurologists. Actually, the agreements in bradykinesia, dyskinesia and tremor assessments were not associated with the intra-case variability of severity, but directly with the symptoms' severity. The most severe PKG symptoms resulted in the lowest agreement. Moreover, the highest symptom severities generally go along with the highest number of events, which engender more detections of events by the neurologists, and as such, a higher likelihood of discrepancy resulting in less agreement. Our results highlight the need for standardizing the reading of monitoring results, especially for the most severe cases, which necessarily need treatment adaptations.

There was no consensus in the direction of the treatment modifications for each patient, even if on average more than 6 out of the 8 neurologists agreed on the therapy direction of the case. Either discrepancy in the PKG reading could not allow for a unique decision, or the information collected was not sufficient. In the trial by Santiago et al., the four study neurologists found that monitoring results did not provide useful information in addition to the visit for 59% of the cases (15). The disparity in the neurologists' experience of the PKG might explain the differences in readings of the results, and thus, decisions on a treatment action (21). Perhaps also, the type of presentation of results may influence the interpretation of the monitoring results. For example, a binary display of PD symptoms, such as dichotomous ON and OFF states, may

not lead to a wide variability of interpretation [\(22\)](#). Our study highlights the need for explicit criteria as the heterogeneity of interpretation might modify decisions in therapeutic actions. Moreover, this heterogeneity triggers the question of reliability when controlled trials involve the interpretation of monitoring results.

Finally, we found a consistent relationship between the integrated data of the PKG (FDS, PTT and PTI) and the dominant therapeutic decisions, and thus explored key elements that may be involved in the automatization of DAT adaptations. Pahwa et al. suggested that target scores should help neurologists to better integrate BWS into clinical practice [\(8\)](#), which may support the adoption of such technology [\(23\)](#). Precisely, Farzanehfar et al. provided guidance to neurologists through the definition of targets in PKG, especially the Percent of Time Over Target which can be provided by PKG, but was not available in our study. They found that monitoring results could influence the therapeutic decision in 61% of cases [\(7\)](#). Another factor that could account for the discrepancies in treatment adaptation agreement was the lack of explicit recommendation to follow published guidelines regarding treatment adaptation in patients with motor complications. Usually, the treating neurologist knows the patient, and no decision depends only on a “virtual” case. The artificial situation that we created might exist in the future with intelligent systems that can directly identify candidates for DAT [\(24\)](#), predict the response to treatment [\(16\)](#), or regulate its delivery [\(25\)](#). A first approach may be an intelligent system that triggers alerts when selected parameters exceed any determined threshold based on BWS monitoring and suggests an intervention by specialists. Such a hybrid system leaves the full decision to the specialists and the possibility of having access to other parameters that the patient would report best. Another more ambitious and innovative approach is a closed-loop system that would allow online adaptations of dopaminergic treatments, for example the apomorphine flow rate, based on continuous measurement of motor parameters from a BWS. A first attempt was performed by Rodriguez-Molinero et al. studying the real-time impact of variations of the apomorphine flow rate on the results of a BWS monitoring [\(25\)](#). The system showed some tendencies indicating improved symptom control and thus is an incentive for further development of closed-loop techniques.

To assist in therapeutic decision making, our work suggests an original approach by selecting relevant parameters from among the information available from a single BWS. Among the strengths of this study, the patient cases represented a variety of situations encountered in PD. According to the PKG instructions, they were described with no or uncontrolled fluctuations, with or without tremor, and close to subjects without PD. In addition, as the goal of our study was to provide latitude for maneuvering and learning about PKG reading in real-life, we purposefully gave no precise instructions to the neurologists, which could have reduced variability in event detection.

Some pitfalls should be considered. First, clinical studies with a larger sample of neurologists and decisions regarding treatment adaptation are needed to further develop the process of criteria selection and the development of automated systems for treatment adaptation. Second, the neurologists' readings might not be entirely replicable due to variability in PKG expertise. Moreover, as they did not know the patients, the neurologists may have required additional information such as nonmotor symptoms. A few studies showed correlations between the objective monitoring of motor symptoms and the appearance of nonmotor symptoms [\(26–28\)](#). Collecting this information via more elaborate systems would be another solution [\(29,30\)](#).

Our findings explore an emergent area in the management of PD. We created situations where neurologists could make decisions based only on BWS reading and found that the automation of treatment adjustments will not be trivial. Although our findings can guide the selection of relevant information from objective monitoring that are related to decisions in therapy adjustments, we cannot consider the reading of monitoring results as a gold standard because of current varying displays of BWS monitoring results and discrepancies in reading. Standardizing the way information from BWS is analyzed may facilitate more consistent interpretations and treatment modifications by PD specialists in routine practice, and in the context of DAT counselling, it would also benefit the implementation of these intelligent systems [\(23\)](#).

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FIGURES

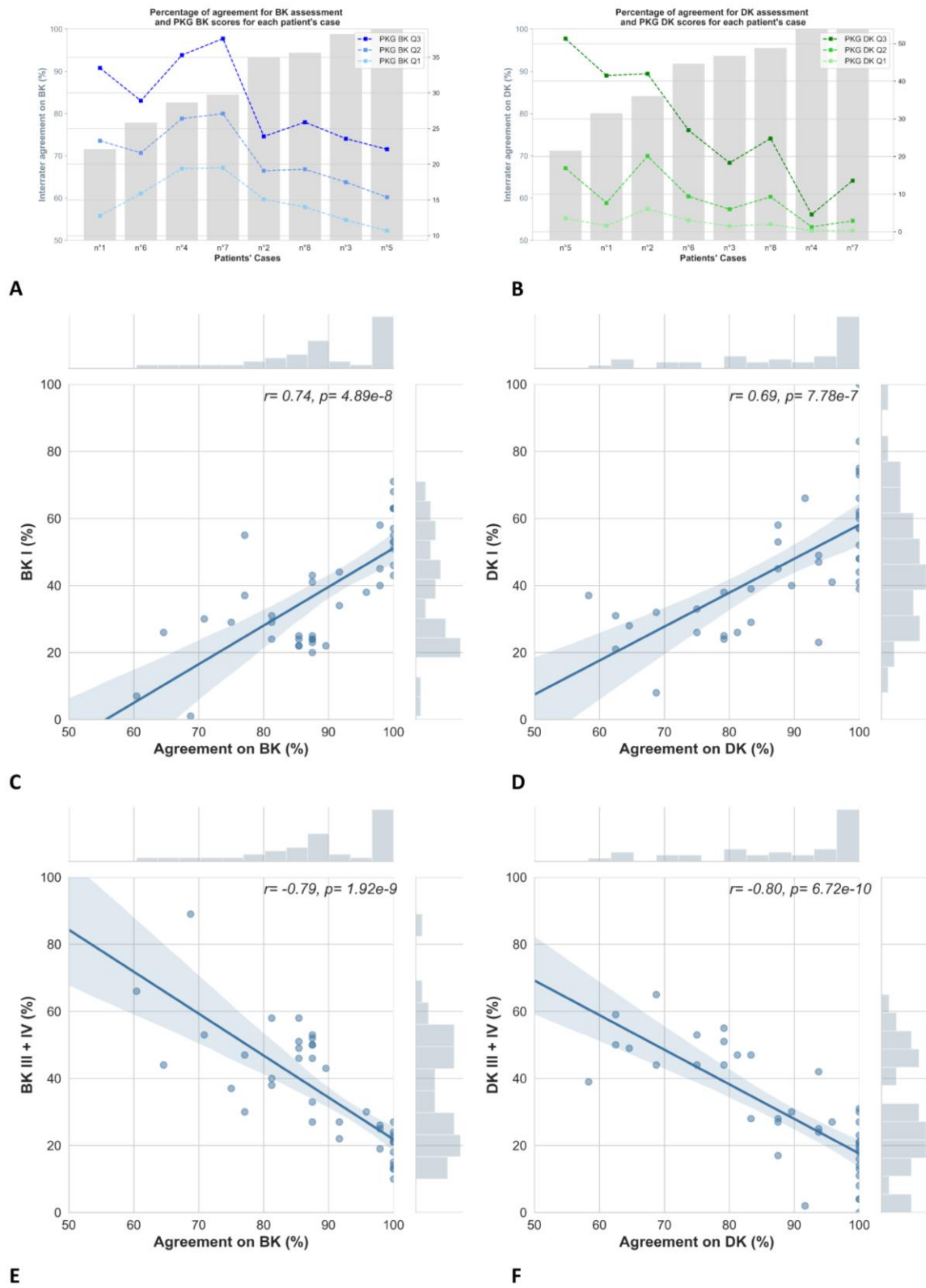


Figure 1: PKG bradykinesia and dyskinesia reading

A and B. Percentage of interrater agreement for each patient's case in bradykinesia and dyskinesia assessment (bars in grey, left Y-axis) and global PKG BKS and DKS as quartiles and median (blue dots for bradykinesia and green dots for dyskinesia, right Y-axis). Patient cases were sorted by agreement in the symptom assessment by raters.

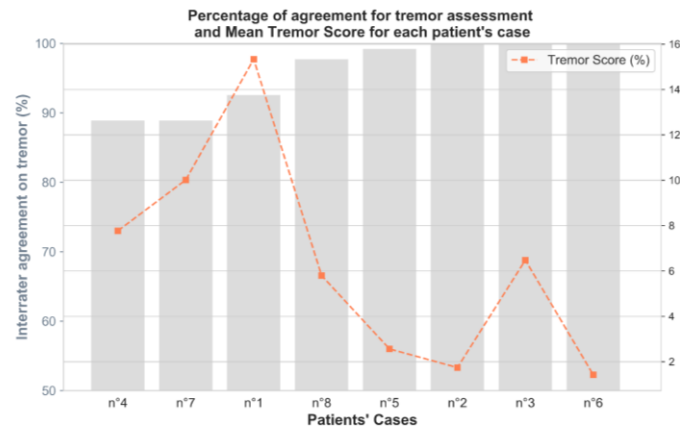
C and D. Representation of the correlation between the interrater agreement in bradykinesia and dyskinesia assessment and the percent of time spent by periods of 3 hours in the lowest level of severity of bradykinesia and dyskinesia, respectively (BK I and DK I).

r: correlation coefficient and p value

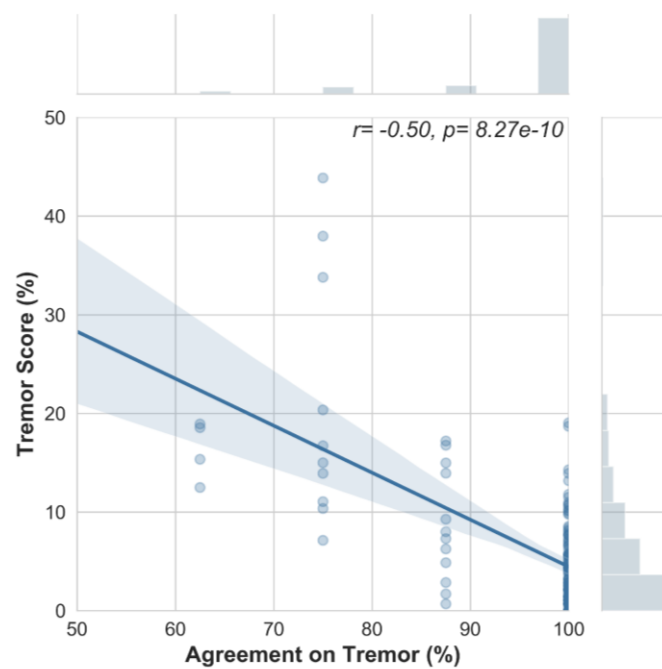
E and F. Representation of the correlation between the interrater agreement in bradykinesia and dyskinesia assessment and the percent of time spent by periods of 3 hours in the highest levels of severity of bradykinesia and dyskinesia, respectively (BK III+IV and DK III+IV).

r: correlation coefficient and p: significance from the Spearman correlation

In C, D, E and F, the dots represent the percentage of agreement in the assessment of the symptom for each percent of time spent in the severity level of the symptom. The fill-lines represent the correlation with confidence intervals in transparency.



A



B

Figure 2: PKG tremor reading

A. Percentage of interrater agreement for each patient's case in tremor assessment (bars in grey, left Y-axis) and Tremor Score (orange dots, right Y-axis). Patient cases were sorted by agreement in the symptom assessment by raters.

B. Representation of the correlation between the interrater agreement in tremor assessment and the Tremor Score. The dots represent the percentage of agreement in the assessment of the symptom for each percent of time spent in the severity level of the symptom. The fill-line represents the correlation with confidence intervals in transparency.

r: correlation coefficient and p: significance from the Spearman correlation

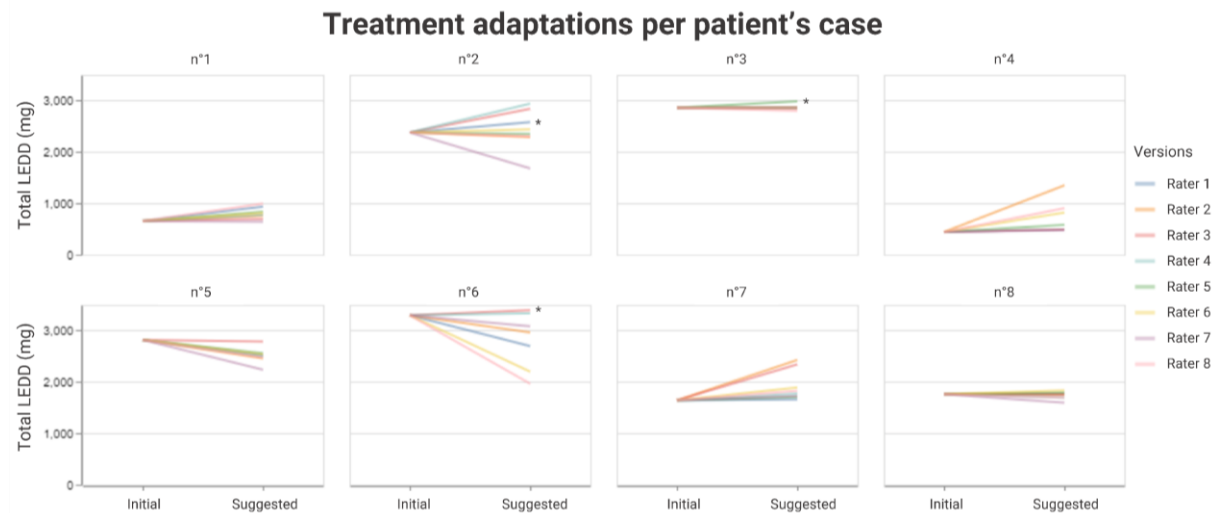


Figure 3: Treatment adaptations per patient case suggested by all raters

One color is attributed to each rater. Evolution between the initial total LEDD (Levodopa Equivalent Daily Dose) and the eight suggested LEDD are presented for each case.

Augmentations of total LEDD suggested by Rater 1 for Case n°2, Rater 5 for Case n°3, and Rater 3 for Case n°6 were only based on the addition of Amantadine, which corresponds to a therapeutic action towards the reduction of antiparkinsonian treatment. They are noted by the asterisk sign (*).

Table 1: Impacts of the patients and PKG information on the treatment modification: increase, stabilization or decrease of total LEDD

	Increase (n= 29) <i>Mean (ic90%)</i>	Stabilization (n= 8) <i>Mean (ic90%)</i>	Decrease (n= 27) <i>Mean (ic90%)</i>
Age	-0.289 (-0.374, -0.210)	-0.099 (-0.183, -0.027)	-0.199 (-0.290, -0.110)
FDS	-0.320 (-0.434, -0.193)	-0.861 (-0.933, -0.788)	0.398 (0.269, 0.510)
PTI	1.011 (0.912, 1.104)	-1.140 (-1.211, -1.064)	-0.590 (-0.708, -0.480)
PTT	1.158 (1.036, 1.302)	-0.232 (-0.330, -0.130)	-1.428 (-1.562, -1.306)
Initial total LEDD	-1.182 (-1.327, -1.076)	0.154 (0.049, 0.261)	0.732 (0.600, 0.871)

mean: estimated effect of the factor from the 1000 iterative resamplings at 80% of the 64 combinations

ic90%: credible interval at 90% from the distribution of the bootstrapping distribution

Supplementary Table 1: Patients cases information

Patients' Cases	n°1	n°2	n°3	n°4	n°5	n°6	n°7	n°8
Gender	M	F	M	M	M	M	M	M
Age (y)	53	68	72	58	53	73	64	70
Weight (kg)	92	41	75	78	70	91	77	73
Height (m)	1.78	1.55	1.70	1.68	1.82	1.81	1.73	1.64
PD duration (y)	16	18	7	4	11	17	7	13
BK PKG Q1	12.8	15.1	12.2	19.4	10.7	15.9	19.5	14
BK PKG Q2	23.3	19.1	17.5	26.4	15.4	21.6	27.1	19.3
BK PKG Q3	33.5	23.9	23.6	35.3	22.1	28.9	37.6	25.9
DK PKG Q1	1.6	6.1	1.5	0.3	3.6	3.1	0.3	2
DK PKG Q2	7.7	20.1	6	1.3	16.9	9.4	2.9	9.3
DK PKG Q3	41.5	42	18.3	4.6	51.3	27	13.6	24.8
FDS	18.1	14.9	10	6.5	17.8	12.9	11.2	12.2
PTI (%)	7.3	1.5	0.4	6	3.3	3.6	12	2.8
PTT (%)	1.1	0.1	0.6	1.3	0.2	0.1	1.2	0.5

Supplementary Figure 2: Example of a patient's case

Information	Values
Gender	M
Age	53 yo
Weight	70kg
Height	1m82
Duration of PD	11 years
Duration of dyskinesias	8 years
Medical History	Toxicomania

A.

Conventional treatment

Treatment Class	On going	Treatment name	Dosage	Posology
L-Dopa	X	Modopar	125	4
Dopaminergic Agonists	X	Requip LP Requip	4 5	3
Anticholinergics	<input type="checkbox"/>			
Amantadine	X	Mantadix	100	2
MAO-B	X	Xadago	100	1
ICOMT	<input type="checkbox"/>			
Apomorphine pen	<input type="checkbox"/>			
Clozapine	<input type="checkbox"/>			
Antidepressants	<input type="checkbox"/>			
Other(s)	X	Durogesic	12	

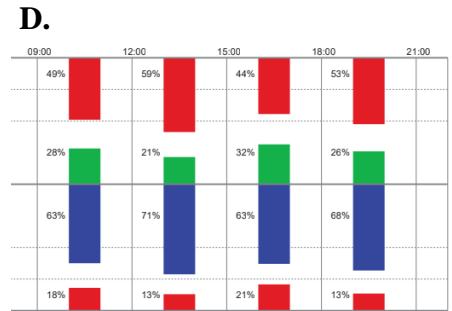
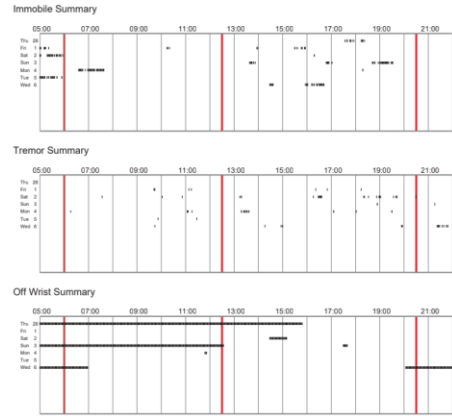
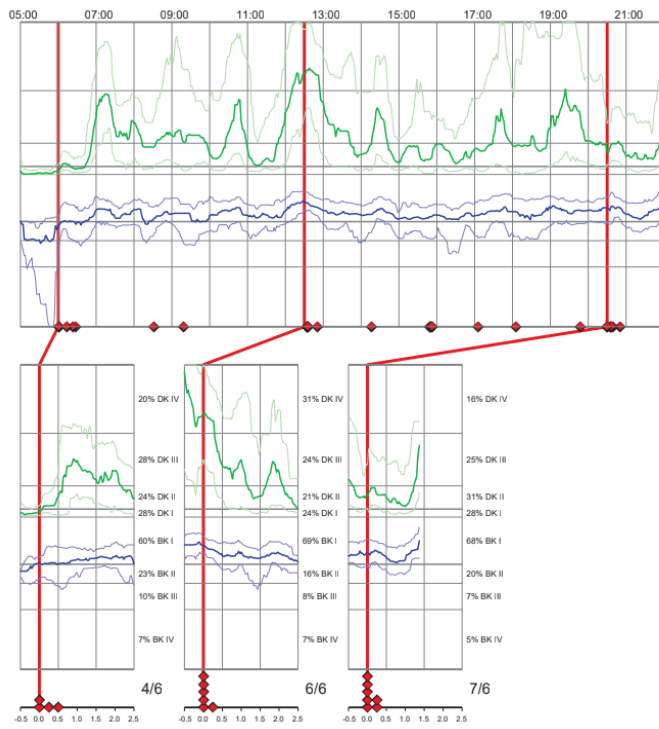
Continuous Subcutaneous Apomorphine Infusion

Duration of treatment per day: **Continuous between 7am-11pm**

Pump infusion rate: **Two flow rates:**

1st = 5 mg/h 2nd = 6 mg/h

B.

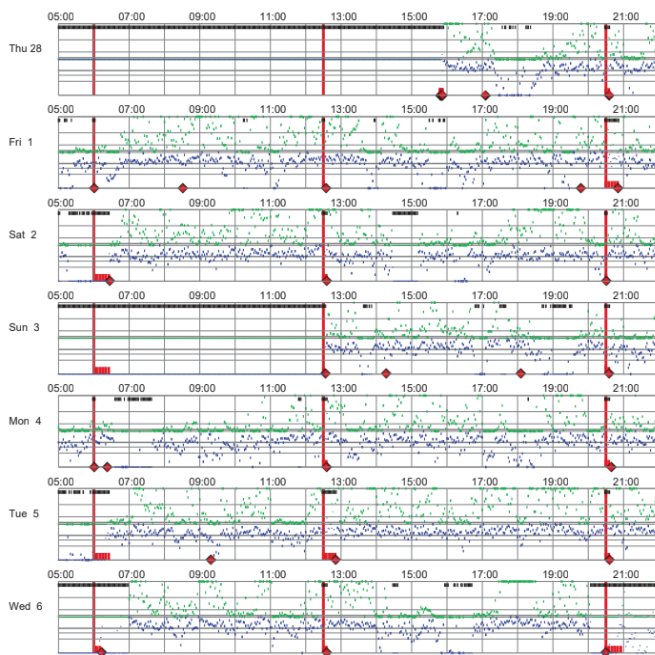


C.

E.

	Patient 5	Control	(Percentiles)
BK (09:00 - 18:00)	10.7 - 15.4 - 22.1	12.7 - 18.6 - 26.1	25 - 50 - 75
DK (09:00 - 18:00)	3.6 - 16.9 - 51.3	0.9 - 4.3 - 16.5	25 - 50 - 75
FDS (09:00 - 18:00)	17.8		
PTI (09:00 - 18:00)	3.3%		
PTT (09:00 - 18:00)	0.2%		

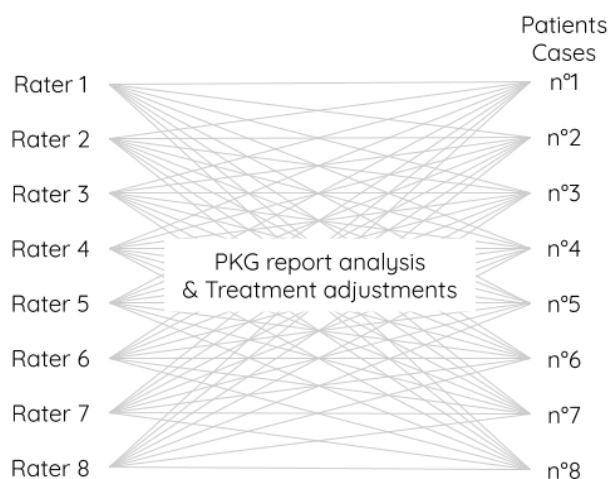
F.



G.

Each patient's case was composed of general information about the patient (A), the treatment prescribed at the time of monitoring regarding conventional and continuous subcutaneous apomorphine infusion (B), and the PKG as it was collected after creation by the proprietary algorithm (C, D, E, F, and G). C is the main graph, from which the continuous parameters BKmed, BK75, DKmed, and DK75 were obtained via standardized methods. D shows three summary graphs for immobile time, tremor occurrence and time with the PKG Watch off wrist. The tremor summary graph was used to create the continuous percent of time with tremor (Tremor Score) via standardized methods. E is the second graph that displays the percentages of time at severity levels I and III+IV per periods of 3 hours, and from which BK I, BK III+IV, DK I, and DK III+IV were collected. F gathers the summarized scores displayed at the end of the PKG, from which the global first, second and third quartiles of the BKS and DKS (BK Q1, BK Q2, BK Q3, DK Q1, DK Q2, DK Q3), and the FDS, PTI and PTT were collected. Finally, G is the detailed evolution of bradykinesia and dyskinesia for each day along the entire period of monitoring.

Supplementary Figure 2: Repartition of the patients cases to the raters



Supplementary Table 2: Percentages of agreement between raters for each symptom analyzed and treatment adaptation decisions per patient's case

Patients' Cases	n°1	n°2	n°3	n°4	n°5	n°6	n°7	n°8
Agreement on BK (%)	71.7	93.4	98.9	82.7	100.0	77.9	84.6	94.5
Agreement on DK (%)	80.1	84.2	93.8	100.0	71.3	91.9	100.0	95.6
Agreement on tremor (%)	92.6	100.0	100.0	89.0	99.3	100.0	89.0	97.8
Agreement on treatment adaptation direction (%)	87.5	62.5	75	87.5	100	75	100	50

Supplementary Table 3: Impacts of the patient's case and the rater on the treatment

modification: increase, stabilization or decrease of total LED

	Increase (n= 29)		Stabilization (n= 8)		Decrease (n= 27)	
	<i>mean</i>	<i>ic90%</i>	<i>mean</i>	<i>ic90%</i>	<i>mean</i>	<i>ic90%</i>
Patients'						
Cases						
<i>n°1</i>	0.474	0.260, 0.768	-0.406	-0.491, -0.288	-0.358	-0.649, -0.155
<i>n°2</i>	0.258	-0.087, 0.534	-0.705	-0.835, -0.533	0.055	-0.227, 0.375
<i>n°3</i>	-0.839	-0.969, -0.671	2.101	1.838, 2.411	-0.599	-0.890, -0.327
<i>n°4</i>	0.720	0.569, 0.855	-0.592	-0.694, -0.449	-0.553	-0.665, -0.421
<i>n°5</i>	-0.773	-0.912, -0.603	-0.609	-0.724, -0.447	1.067	0.869, 1.248
<i>n°6</i>	-0.331	-0.626, -0.125	-0.684	-0.797, -0.531	0.683	0.448, 0.972
<i>n°7</i>	0.768	0.624, 0.900	-0.379	-0.459, -0.278	-0.609	-0.723, -0.473
<i>n°8</i>	-0.416	-0.726, -0.120	0.740	0.314, 1.121	0.121	-0.194, 0.470
Raters						
<i>neuro1</i>	-0.224	-0.412, -0.030	0.637	0.081, 1.014	-0.157	-0.420, 0.114
<i>neuro2</i>	-0.229	-0.417, -0.032	-0.067	-0.520, 0.225	0.205	-0.066, 0.459
<i>neuro3</i>	0.110	-0.204, 0.365	0.630	0.044, 1.017	-0.502	-0.760, -0.218
<i>neuro4</i>	0.451	0.113, 0.765	-0.076	-0.515, 0.227	-0.520	-0.879, -0.168
<i>neuro5</i>	0.121	-0.189, 0.359	-0.766	-0.932, -0.409	0.201	-0.103, 0.512
<i>neuro6</i>	0.473	0.174, 0.733	-0.066	-0.521, 0.221	-0.510	-0.748, -0.244
<i>neuro7</i>	-0.611	-0.841, -0.268	-0.068	-0.521, 0.231	0.532	0.198, 0.839
<i>neuro8</i>	-0.230	-0.420, -0.020	-0.760	-0.927, -0.419	0.558	0.267, 0.807

mean: estimated effect of the factor from the 1000 iterative resamplings at 80% of the 64 combinations

ic90%: credible interval at 90% from the distribution of the bootstrapping distribution

4.2 Detailed analysis of PKG reading and therapeutic adaptation

The analysis of the PKG® reading and therapeutic adaptations have been further expanded to complete the main results with a similar methodology. Additional outcomes are presented here, and specification on the methodology employed is available in Supplementary Material V.

4.2.1 PKG reading

Percentages of time (between 5 A.M. and 10 P.M.) spent in each degree of severity in BK and DK (BK 1, BK 2, BK 3, BK 4, DK 1, DK 2, DK 3, and DK 4) are integrated information directly provided by the PKG and reflect the severity of symptoms. Those scores are detailed for each patient case in Supplementary Table 5 in Supplementary Material VI. Spearman correlation studies showed relationships between the agreement in the symptom assessment and BK 1, BK 2, BK 3, BK 4, DK 1, DK 2, DK 3, and DK 4 ($n=8$). The interrater agreement in bradykinesia assessment was significantly correlated with BK 3 ($r=-0.81$ and $p=0.01$), but it was not associated with BK 1, BK 2, and BK 4 ($r=0.68$, $r=0.18$, and $r=-0.65$, respectively with $p>0.05$). In parallel, the interrater agreement in dyskinesia assessment was significantly correlated with DK 4 ($r=-0.96$ and $p<0.001$), but it was not associated with DK 1, DK 2, and DK 3 ($r=0.69$, $r=0.23$, and $r=-0.37$, respectively with $p>0.05$).

The positive link between interrater agreement in symptom assessment and the lowest severity levels was also opposed to the negative link between the interrater agreement in symptom assessment and the highest severity levels (BK 3 and DK 4). Thus, those results reinforced the previous conclusion regarding PKG® reading: the most severe PKG® symptoms resulted in the lowest agreement.

Finally, agreements in bradykinesia, dyskinesia, and tremor were studied in connection with the summarized scores of PKG® for each patient case ($n=8$). Agreement between bradykinesia

assessment and PTI were not associated ($r=-0.58$, $p=0.13$), agreement between dyskinesia assessment and FDS were significantly associated ($r=-0.90$, $p=0.003$), and agreement between tremor assessment and PTT were significantly associated ($r=-0.94$, $p<0.001$). In addition, agreement in tremor assessment was significantly correlated with PTI ($r=-0.86$, $p=0.006$). These scores might be adequate to summarize PKG® information that will serve the decision of action on treatment, or a hypothetical closed-loop system.

4.2.2 Treatment adjustments

In addition to the results on total LEDD adaptation, we present an individual study of conventional and CSAI treatments.

Among the 64 possible suggestions of treatment modifications, 16 had no change regarding oral treatments and 19 had no modification of the CSAI therapy (not for the same patients). Conventional LEDD changed from 82% to 313% of its initial value (Figure 19), and apomorphine LEDD changed from 40% to 300% of its initial value (Figure 20).

Suggestions of apomorphine LEDD change or conventional LEDD change were not in the same direction for every patient case. The orientation of the total LEDD modification depended on a balance between the main orientation of treatment modification given to apomorphine LEDD and to conventional LEDD. For example, the main tendency in treatment modification for Case n°5 was a decrease of apomorphine LEDD (agreement of 87.5%) and a stabilization of conventional LEDD (agreement of 62.5%) (Table 1). However, the resulting actions regarding total LEDD of this case was a decrease for 100% of the raters.

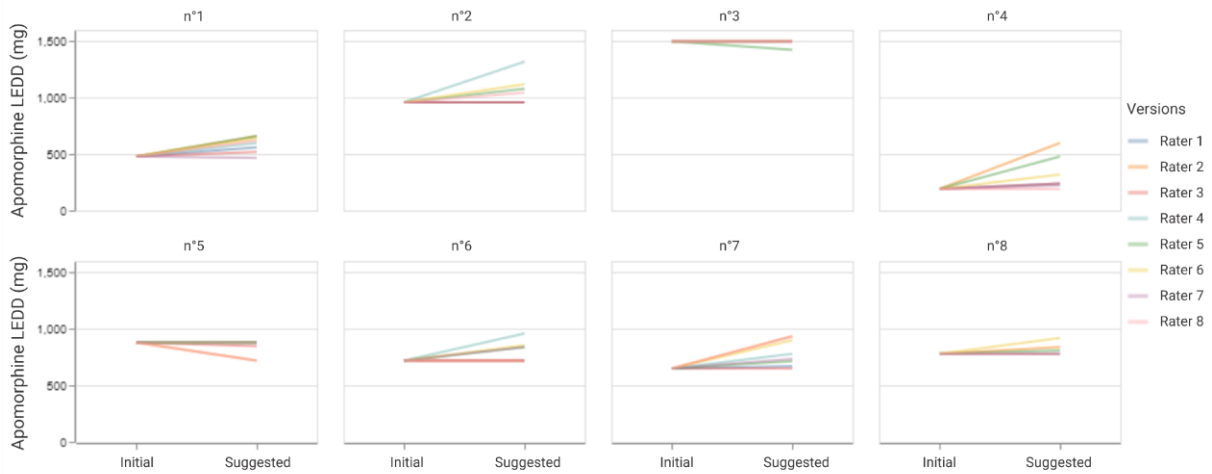


Figure 19: Suggestions of apomorphine LEDD adaptation per patient’s case and for each rater

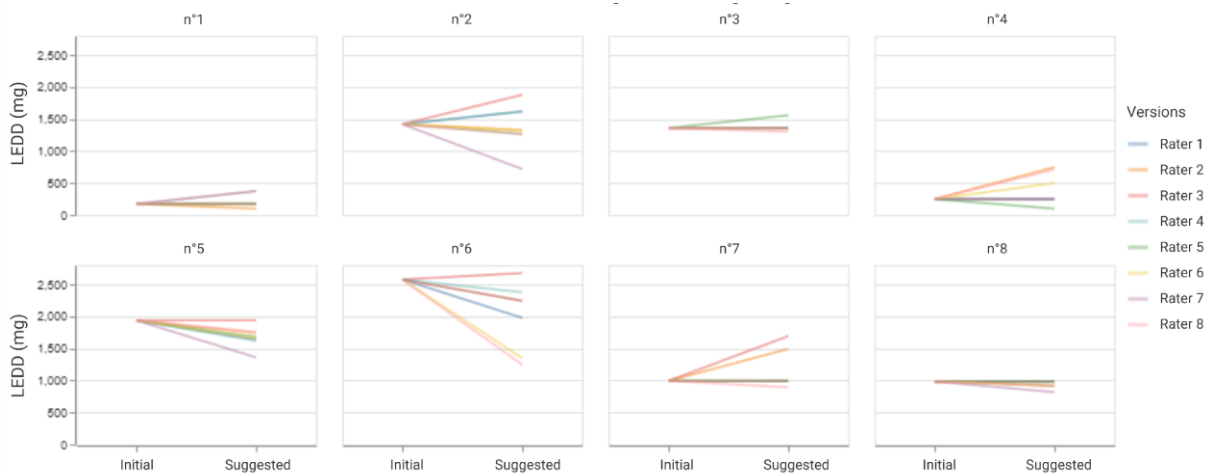


Figure 20: Suggestions of conventional treatments LEDD adaptation per patient’s case and for each rater

Patients’ Cases	n°1	n°2	n°3	n°4	n°5	n°6	n°7	n°8
Agreement on apomorphine LEDD (%)	87.5	50	87.5	75	62.5	50	87.5	62.5
Agreement on conventional LEDD (%)	62.5	62.5	87.5	50	87.5	75	75	62.5

Table 1: Percentages of agreement between raters for apomorphine and conventional treatments adaptation per patient’s case

Agreement between raters for the actions on both treatments were consistent although not unanimous.

4.2.3 Link between the case analysis and treatment adjustments

In the questionnaire (Supplementary Material VII), the raters had to clarify whether they found the symptom significant in each case, and if it was decisive for their suggestion of treatment modification. Among the 64 combinations, the raters said that bradykinesia was significant in 42 cases, dyskinesia in 44 cases, and tremor in 26 cases. The raters said that they suggested treatment modification to suit severity of bradykinesia in 36 cases, severity of dyskinesia in 39 cases, and severity of tremor in 18 cases. Then, despite a symptom severity assessed as significant, the raters did not use this evaluation to suggest treatment modification for all cases.

4.2.4 Qualitative analysis of the neurologists answers

The questionnaire allowed raters to specify comments on their decision and/or remarks to be transmitted to the patient (Supplementary Material VII). We considered their notes to further describe the link between the PKG reading and treatment adaptation.

Currently, the interpretation of quantified measures without being aware of the therapeutic objectives is difficult. The raters described their interpretation of the PKG in the comments section in 46 cases. Some raters asked for a reference (monitoring before/after change of therapy or in ON *vs.* OFF state) or a customization of the algorithm to the patient to better understand what the results mean for a specific patient, and then adapt the treatment accordingly. Neurologists also expressed the need for the information on other symptoms in twelve cases. Especially, they asked for indication on non-motor symptoms and the presence of impulse control disorders that may be very important in treatment adjustments, but are not directly provided by a BWS monitoring. Also, neurologists used the comments section to

virtually provide information to the patient. In four cases, they justified the treatment adaptation, in five cases they felt the need to ask questions to the patient, and in six cases they shared therapeutic education advice. Interestingly, in two cases, the raters put conditions on their suggestions of treatment modification following the interview with the patient. This statement shows that adjusting treatment without knowing the patient may be difficult and trigger doubts among PD experts, which may also be challenged in the case of closed-loop systems.

4.3 PD management with BWS is feasible, but can we automate it into a closed-loop system?

According to the neurologists, other information would have been useful in the decision for treatment action from the results of a BWS, which might have increased consistency in agreements. For instance, BWS results have already been associated with several NMS (van Wamelen et al. 2019), but all information about PD may not be encoded by the BWS. The variability of PD symptoms and their manifestations among patients is wide and closed-loop systems might not capture such human variations. The implementation of an adaptive CSAI should consider in what situations actions on treatment may be realized without direct access to a patient interview, and how to act accordingly if so. The development of systems for automated treatment adaptations in PD will necessitate the selection of information from objective monitoring, which could influence the accuracy of therapeutic decisions. Yet, the technology behind objective monitoring is not uniform, and BWS results show various PD symptoms that may trigger different interpretations into clinical decisions. Several types of scores from different BWS may engender various therapeutic decisions, and maybe diverse clinical impacts on a patient health. Thus, our results advocate for the importance of standardization in the reading of monitoring results, for instance via the selection of BWS

criteria and guidelines to help the process of interpretation. Ideally, the parameter-of-interest that would generate the decision for actions on treatment should be decided by PD specialists in accordance with BWS technical solutions. Then, exploring the possible parameters-of-interest that would contribute to an adaptive CSAI system is a fundamental step because there is currently no gold standard among the numerous features recorded by a single BWS. Our study highlights that closing the loop in PD is not impossible, but may require additional knowledge before its application in treatment management, which suggests the possibility of an intermediate solution such as a hybrid-loop system.

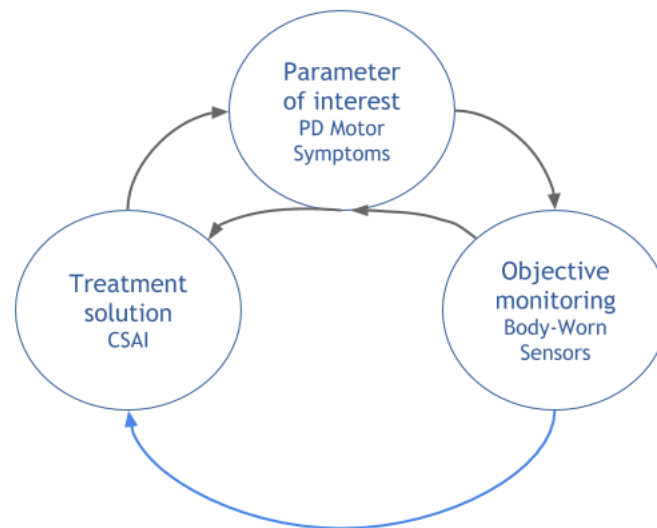


Figure 21: Scheme of adaptive CSAI based on BWS monitoring of motor symptoms in line with a closed-loop system. The blue line represents the link we have studied in this section of the manuscript

5. Discussion and perspectives

The objective of our work was to analyze the possibility of implementing a closed-loop approach in the follow-up of patients with Parkinson's disease. Toward this aim, we studied the links between each of the possible components of such a loop and each link was examined in both directions.

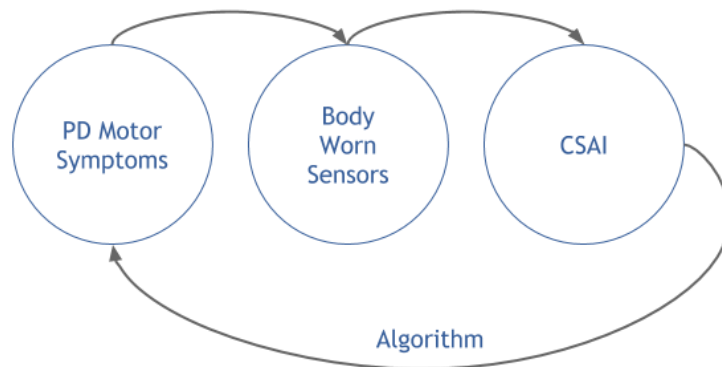


Figure 22: A closed-loop system in Parkinson's disease

Our first investigation supported the positive impact of CSAI on PD motor symptoms and the modest influence of motor symptom clinical scores on decisions for CSAI. On the one hand, CSAI was shown to be effective in improving the symptoms of patients with advanced PD. Poor quality of life may be improved after two years of CSAI, and patients tolerate treatment well with positive self-reports on its effects. Meanwhile, we worked on a new approach by looking at the influence of disease characteristics and the patient on treatment decisions. Surprisingly, except for apathy regarding the initiation of CSAI, no clinical scores of symptoms had a direct and significant impact on therapeutic adjustments. Additional work may help calibrate a potential therapeutic decision algorithm from the parameters of interest.

Our second approach oriented our gaze by considering the human perspective by exploring the user experience of BWS. We exposed the positive perceptions of patients and healthcare professionals, and highlighted enthusiasm but also needs regarding the implementation of BWS

in PD follow-up. This part of our work expanded the reliability of BWS monitoring in PD care, the technical and human components involved in BWS are conclusive.

Our third and last study was a first approach to the automation of CSAI from BWS measurements. The interpretation of the use of BWS results by neurologists has provided us with the first clues about the determining elements of continuous and objective measurement for therapeutic decisions. In addition, direct and precise links have yet to be made to automatically manage therapeutic actions from BWS measurements alone in the context of a closed-loop system.

The results of our three investigations show that connecting PD motor symptoms, BWS and CSAI is feasible. BWS could be a relevant tool for a more personalized follow-up of patients, or as a contribution of additional information to reduce for example the burden of hospitalizations. However, standardization of devices and algorithms is required to reduce the risk of variability in the interpretation of results and to indicate clear instructions for the correspondence of the measurements with the therapeutic actions to be taken.

This work considered the establishment of a closed-loop system in PD from different points of view on components that already exist. However, there are limits to our work. By considering each component of the closed-loop and each link independently, we did not study the feasibility of a complete system. Indeed, our work on a closed-system was observational and did not rely on an interventional study, which limits the scope of our conclusions. Moreover, we did not address the building of an algorithm. Further work should be performed to model therapeutic actions from a board of experts who interpret data from continuous and objective measurements. Once this is materialized, it will be necessary to study the different aspects of the automation of therapeutic actions based on BWS.

Until now, the management of care in PD has followed an open-loop pattern that requires human interaction at various levels. Following our analysis, we can compare this open-loop to

what an intelligent closed-loop system could provide. Thus, we will discuss here the description of the parameters of interest in PD, the sensors allowing such measurements, and the treatment solution which will have an impact on those parameters. Finally, we will return to the process behind therapeutic actions as a function of BWS measurement by comparing the current management of PD to the version that could exist in a closed-loop system.

5.1 Parameter-of-interest: motor symptoms

In the management of PD patients, the major point of interest is the experienced symptom. Whatever its origin, or its type of manifestation, the symptom is the target that clinicians seek to eliminate or reduce. The symptoms of PD are numerous and vary from patient to patient. Currently, the follow-up of PD is comprehensive and considers all types of symptoms, motor or non-motor. The care is often multidisciplinary and there are many stakeholders (neurologist, general practitioner, physiotherapist, speech therapist, *etc.*). When it comes to tailoring anti-Parkinsonian therapy to suit a patient's needs, the healthcare team takes into account any PD-related symptoms that need improvement. The consideration of such diverse symptoms sometimes brings into play different means of evaluation, which are dependent on human expertise (either by patient intervention or by healthcare professional evaluation). Current evaluations may be subject to a risk of imprecision. In the hypothetical follow-up of PD patients with a closed-loop system, the measured parameter would necessarily be dependent on the algorithm of the device involved in this system. A PD point of interest should then be determined before setting up a closed-loop system, which will be a trade-off between manufacturer, PD experts, and payers. In addition, the multitude of symptoms in PD would require consideration of the integration of multiple measurement sensors in a closed-loop system. Due to their intrinsic nature, certain symptoms remain very difficult to measure continuously without medical supervision when using a physical sensor, such as for example

fatigue or cognitive impairment. Therefore, another possible perspective is that the occurrence of some PD symptoms is closely related to the appearance of other more easily measurable symptoms. Indeed, if their appearances and fluctuations are closely related, the precise improvement in motor symptoms might influence that in NMS. It would then be sufficient to measure the motor symptoms through a BWS to manage the two types of symptoms. However, the hypothesis of an exact correspondence between motor and NMS has not yet been validated and, if it exists, it is likely that consideration of one or the other type of symptom is not sufficient for correct treatment actions. Finally, considering the intra- and inter-variability of symptoms among patients is important. The fairly universal definition of motor symptoms may not necessarily be the same for everyone, both in terms of physical appearance and perception. However, for now, the patient's perception of the symptom is an absent dimension of BWS. Cases of closed-loop systems involving patient participation through self-questionnaires (as for example in the PERFORM system approach (Tzallas et al. 2014)) would be a way of considering this variable which sometimes strongly impacts treatment decisions. However, this type of system would therefore no longer be based on a completely automated therapeutic action. As such, it may be that intelligent systems could one day facilitate calibration of troublesome and non-troublesome symptoms.

The increasing interest in the evaluation of PD symptoms with objective measurement will undoubtedly further refine the knowledge about their kinematic description, which is useful for the enhancement of BWS algorithms. Moreover, precise knowledge among healthcare professionals about how a BWS captures and then translates symptoms is an essential step in the implementation of a hypothetical adaptive CSAI from BWS in routine practices.

5.2 Monitoring area: Body-Worn Sensors (BWS)

In the case of a closed-loop with BWS and CSAI, the parameter of interest would be limited to motor symptoms, and more precisely to the specific parameters of the BWS selected for this loop. Measurements of PD motor symptoms by BWS have been validated but are nuanced by the performance of integrated algorithms, and also by the position of the sensor on the body. However, unlike human performance which may vary (for example, a patient's ability to complete a diary may decrease over time (Papapetropoulos 2012)), a BWS will normally be calibrated to measure in the same way regardless of its duration of use. Accordingly, BWS is a robust and consistent way to assess motor symptoms over the long term and under real-life conditions. In this work, three different systems were presented to healthcare professionals and they could express a possible choice of one system or another according to the symptoms being measured and the presentation of the results. As the perceptions of the three sensors were very similar from patients' perspectives regarding usability and acceptability, the choices of healthcare professionals could be based primarily on recording goals. The descriptions of each available BWS makes it possible to conjecture on the most relevant system for a specific patient's profile before its use. However, a comparative study on the measurements of diverse BWS in real life would help formalize clear instructions of use. Moreover, standardization of BWS validation is a major requirement for broader adoption (Brognara et al. 2019; Domingos and Ferreira 2016). As discrepancies existed in a unique BWS, several different systems could also engender disparities in the reading and therefore in the data interpretation. Collaborative work between developers of new BWS for PD continuous monitoring and healthcare professionals would be an advantage in the adoption of these tools in current practice. It is also essential to take into account patient as users. Further, the constant miniaturization of available technologies is in favor of further improved adhesion. Sensors in the form of patches are in the developmental phase and could measure symptoms of PD with accelerometers and built-in

algorithms like BWS, as well as vital signs (Lonini et al. 2018; Chan et al. 2013). The current limiting factors are around the power supply of such a device because batteries are not yet sufficiently reduced in size, and their use is therefore still restricted either in time or in space and do not yet allow monitoring to be carried out in the long-term at home. Sensorless movement measurements are also becoming more precise. Remote recording systems can be placed in various areas of a house to capture movements and analyze behavior (Cook, Schmitter-Edgecombe, and Dawadi 2015). These solutions are still at the early stages of development and studies are necessary before validating these measurement techniques for objective patient monitoring.

Currently, while NMS are crucial in PD, few devices currently allow a real view of their quantified measurement over a long period of time and in ambulatory conditions. We wanted to test the feasibility of an objective recording of parameters allowing the evaluation of PD NMS using a portable device that would be adaptable to outpatient measurement. This study is entitled *“Accelerometer-based measures and analyses of gait and respiratory parameters: towards a new assessment for Parkinson’s disease patients”* and is presented in Supplementary Material VIII. In the experiment on six subjects without PD, we were able to conclude that it is possible to measure parameters related to breathing to those of body motion. The polygraphy technique that was used demonstrated differences in the signals collected at rest and during moderate activity. It is likely that this type of measurement can allow study of variations in respiratory parameters in PD patients during activities of daily living. Thus, it would then be possible to analyze indirect effects of respiratory disorders experienced by patients during unsupervised behavior, that is to say over extended periods of time at home compared to the usual tests carried out during consultations. Finally, although this study was limited to a few healthy subjects and one type of NMS, it highlighted the prospect of an objective measurement of non-motor symptoms, which could be performed in outpatient conditions. Meanwhile, the

device involved should be further simplified, for example incorporated into clothing, to allow for continuous recording and be integrated into a closed-loop system.

Currently, technological solutions for capturing PD symptoms exist even if certain limits may be an obstacle to the concrete implementation of a closed-loop system. In the first place, work on the standardization of BWS could help with more widespread adoption of this technology, and further investigations on objective and continuous measurement of NMS would be an advantage for a more complete closed loop.

5.3 Treatment solution: CSAI

Currently, several therapeutic solutions exist for the management of PD patients. These antiparkinsonian treatments are also increasing in number thanks to progress in research. In addition, the variability of the combinations that can be proposed to patients leads to an even greater number of therapeutic strategies. Recommendations exist based on patient profiles, and the performance of DAT for patients with advanced PD is known. In routine care, neurologists have the opportunity to choose the most appropriate treatment for a given patient from among all the possibilities. The antiparkinsonian treatment can be adapted according to the needs and readjusted if necessary based on the effects observed on the targeted symptoms and the possible adverse events. In a closed-loop system without human intervention, conventional oral treatments cannot be adapted automatically, although prescriptions could be suggested by the algorithm. In comparison, DAT offer the possibility of adjusting parameters continuously and even remotely. Apomorphine pumps could receive instructions to change delivery parameters on an ongoing basis. Thus, they might also be almost ready for integration into a hypothetical closed-loop system. To the best of our best knowledge, no LCIG automation test has yet been performed. But since the device is very similar to apomorphine pumps (Pablo Martinez-Martin

et al. 2015), its integration into a closed loop system would certainly require the same processes as the CSAI for improving the pump and the means of communication.

Although a closed-loop with a DAT solution would be limited in the variety of therapeutic choices available for action, it may be sufficient to adjust the therapeutic actions with a single solution. One difficulty in the engagement of multiple stakeholders in PD care is that they may not be aligned regarding the target symptom(s), and on the capability of the available treatment to improve such symptom(s). Thus, the current follow-up leaves some room for trade-off, but also ambiguity on the objective of a therapeutic adjustment. A closed-loop system would shape a more constrained system where one or a few symptoms will be clearly identified as a target and used to trigger actions on treatment. Moreover, the interpretation of the treatment impact on symptoms is based on the medication prescription, which may differ from the actual doses taken if the patient is not compliant to the treatment. A closed-loop system would ensure the conformity between prescription and reality in a patient's life. Additionally, it has already been shown that a single therapeutic approach can significantly improve the symptoms of PD (Shannon et al. 1997; Stern et al. 2004; Parkinson Study Group 2003). Monotherapy with LCIG and CSAI has also demonstrated evidence in terms of safety and efficacy in improving fluctuations and quality of life compared to polytherapy (D Nyholm, Holmberg, and Jansson 2005; Manson, Turner, and Lees 2002). Thus, we can hypothesize that CSAI, automatically adjusted by an advanced algorithm based on symptom measurements, could be effective and promise even better symptom improvement and quality of life.

5.4 Decisions for action on treatment: algorithm

A loop system already exists in the routine monitoring of patients. Indeed, symptoms are observed, and then therapeutic actions are proposed by health professionals who evaluate again the evolution of symptoms in response to this treatment action. From a closed-loop point

of view, this can be considered as retro-control. Therapeutic adjustments are reproduced in this way throughout the patient's life with the disease. However, this loop is open, it is not automated or optimized in real time. When setting up DAT treatment, we may observe a pattern identical to the automation of a process. The system is set up with a first action involving a significant change over a short period of time, and, then, it is more precisely adjusted by retro-control, or feedback, over the long term. For example, the results of our work illustrate these two different regimes after the establishment of the CSAI (Virbel-Fleischman, Houot, et al. 2020). We revealed an important first action reflecting the modification of treatment at initiation (increase in total LEDD in Figure 1 of this paper, for example), and smaller adjustments during the two years of follow-up based on feedback. This loop could evolve at different levels with the help of new technologies.

In particular, human involvement in this loop imposes time constraints. The therapeutic actions are dependent on the consultation or hospitalization schedules. By integrating remote monitoring with continuous information from BWS symptom measurements, the time between these therapeutic actions could be reduced. However, the temporal nature of the therapeutic effects on symptoms is not yet well defined. Currently, the time between consultations makes it possible to observe the impacts of therapeutic actions in hindsight. We can imagine two possible temporalities of adaptive CSAI. One option could copy the current scheme of decisions on treatment: first, motor state monitoring by the BWS during a selected period of time according to the feedback capacities and clinical validity, and second, the therapeutic action triggered by the CSAI pump to respond to the measured needs (Godoi et al. 2019). Another option would be to trigger real-time adjustments to directly respond to a symptom measured by a BWS, or even prevent it with warning signs. The feasibility of modifying the delivery of the apomorphine pump based on the patient's motor status has not yet been sufficiently investigated. Likewise, it would be advantageous to be able to prevent OFF or FoG states by

adapting the treatment received by the patient upstream. This temporality would in all cases depend on the ability of the BWS to detect a symptom and on the performance of the algorithm to trigger an action thanks to the CSAI pump. For the moment, studies are more focused on aDBS, but it would be appropriate to study the impacts of treatments by CSAI, or LCIG, at different and shorter time frames than what is usually observed.

On the other hand, considering the biases of PD assessment, using an objective and standard parameter to judge a patient's condition would already allow for optimization of the current monitoring loop. However, in parallel with the increase in the number of BWS available, their use is still not fully democratized in current care practices. Although MDS advocates access to recording results to monitor PD patients, clinical evidence for the positive impact of BWS on patient condition is still too scarce (Espay et al. 2019; Johansson, Malmgren, and Alt Murphy 2018; Woodrow 2020). In parallel, in-depth knowledge of how to interpret the results of BWS by PD specialists would allow for a better structure in the therapeutic adjustment algorithm of the hypothetical closed-loop system. Indeed, a precise correspondence must be constructed between the objective measurement of a motor symptom by a BWS and the therapeutic action to be triggered with CSAI. At this time, this correspondence has not been given or validated.

Finally, considering the available technology for BWS monitoring and CSAI, and also with the missing information regarding a decisional algorithm between BWS and CSAI, an intermediate solution might be a hybrid loop. Before gathering the required answers and validating the hypotheses for setting up a closed-loop system, a hybrid loop could be implemented with BWS, CSAI, and an external intervention for human verification. A hybrid loop would take advantage of the technology that is ready and would let PD specialists prevail over the therapeutic decision. A hybrid loop would also leave the possibility of collecting other information from other tools or directly from the patient. Indeed, the availability of BWS results does not exclude the use of other measurements sources, such as questionnaires (Tzallas et al. 2014) or in particular intuitive e-diaries (Vizcarra et al. 2019). Even if technologies are not necessarily part of the daily life of patients with PD today, increasingly they will be in regular contact with new technologies due to the proliferation of devices such as smartphones (Dorsey, Glidden, et al. 2018). Also, a hybrid loop system could be implemented with haptic stimulation triggered by the measurement of a symptom with BWS (Albert Sama et al. 2014) or the triggering of visual or auditory cues (Sweeney et al. 2019). All of these tools can participate in the individualization of patient follow-up, by better capturing the experience of the disease and thus offering the most appropriate treatment (Bhidayasiri et al. 2020). By handling devices such as BWS or connected objects directly at home, patients may feel more actively engaged in their care path. Importantly, making patients actors in their disease is a pledge toward decisive progress in the management of PD. Finally, whatever the devices that compose a closed-loop system or its characteristics, it is an approach that places the patient at the center, progressing towards personalized follow-up, just as telemedicine aims at a larger scale (Rajan et al. 2020; Rovini, Maremmani, and Cavallo 2019). Indeed, we have seen the opportunities for reducing hospitalizations or consultations thanks to the contribution of BWS. Home monitoring using BWS is also a way of reducing disparities in access to expert care and also of reducing health

costs (Cubo et al. 2017; Achey et al. 2014). Interestingly, the need for this kind of remote monitoring dramatically increased during the COVID-19 pandemic (Stoessl, Bhatia, and Merello 2020). Alternative methods to the routine care of patients with chronic pathologies appeared more than necessary during this unprecedented crisis. Telephone calls, emails or video consultations were widely used (Hassan et al. 2020). The availability of remote recording technologies also supported this complex and dynamic period (Bloem, Dorsey, and Okun 2020; Papa et al. 2020). In this situation, and for PD patients, a closed-loop would have been of great interest for continuous management of the disease while reducing the need for inpatient visits. In sum, the standardization of BWS, the preparation of CSAI pumps, and the validation of a consensus on the correspondence between objective monitoring and apomorphine delivery remain fundamental investigations to put into action.

6. Conclusion

This work sheds light on the opportunities and challenges in a new paradigm regarding PD patients where there is follow-up through a closed-loop system. As research advances, new technologies can be utilized in the management of PD and offer numerous promising advantages to complement current care. Especially, since the early 2000s, many reviews and studies have advocated for the use of BWS monitoring to improve the quality of therapeutic decisions, and some have broached the closed-loop system approach. In this project, we intended to observe this possible new model of care from different perspectives. We have considered the links between each of the closed-loop system components, in a bidirectional way, and proposed a view on each situation in order to better support the building of such a system for PD. Thanks to the three studies presented here and the literature analysis, a conclusion can be made that technology is still immature in each domain, a hybrid loop is most likely to be appropriate in the near future for PD patients. Accordingly, this intermediate system warrants substantial progress to bridge the gaps in PD management and knowledge.

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Supplementary Material

I. Long-term effect of apomorphine infusion in advanced Parkinson's disease: a real-life study [Submitted] (Meira et al. 2020)

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ABSTRACT

Long-term effects of continuous subcutaneous apomorphine infusion (CSAI) on Health-related quality of life (HRQoL) and predictors of CSAI discontinuation are poorly known. We evaluated consecutive advanced Parkinson's disease patients over 24 months after CSAI initiation, using the 39-item Parkinson's disease Questionnaire (PDQ-39) as the primary endpoint. We determined predictors of CSAI discontinuation and HRQoL improvement using multiple regression analysis. Among the 110 subjects evaluated over a two-year period, 35% discontinued CSAI. In those who continued treatment, HRQoL remained stable with a sustained reduction in motor fluctuations. The effect on dyskinesias was mild and transient. PDQ-39 was the only baseline predictor of HRQoL improvement after two years of treatment. The presence of dyskinesias, poorer psychological status, shorter disease duration, male sex and worse OFF-state were predictors of discontinuation. Best candidates for CSAI are patients: (i) with a poor baseline HRQoL, (ii) who have marked motor fluctuations (iii) in whom dyskinesia are not the main complaint.

INTRODUCTION

Oral dopaminergic therapy is effective in controlling motor manifestations in early Parkinson's disease (PD).¹ With disease progression, motor complications emerge. This reflects a combination of progressive nigrostriatal nerve terminals loss and the pulsatile nature of oral levodopa treatment.^{2,3} Motor complications comprise motor fluctuations and dyskinesias. Attempts to control motor fluctuations with oral medication tend to worsen dyskinesias.²

Motor fluctuations can be managed with continuous dopaminergic drug delivery using either continuous subcutaneous apomorphine infusion (CSAI) or Levodopa-Carbidopa Intestinal Gel (LCIG).^{4,5} Apomorphine is a dopamine agonist with affinity for D1 and D2 receptors.⁶ Several uncontrolled studies have highlighted the efficacy of apomorphine in managing motor complications^{7,8,9} and non-motor symptoms^{10,11,12,13} in patients with advanced PD. More

recently, the efficacy, tolerability and safety of CSAI was demonstrated in a short-term, large, prospective, randomized, placebo-controlled study.¹⁴ The magnitude of the treatment effect on motor fluctuations was in the same range as that observed with LCIG.¹⁵

Despite low internal validity, real-life studies represent an interesting option to study long-term effects of a treatment and the clinical relevance of randomized controlled trials (RCT) findings. Health-related quality of life (HRQoL) is a meaningful outcome measure as it captures patient-centered issues such as daily life functioning and medication-related adverse effects.

Positive short-term effects of CSAI on HRQoL have been observed using Parkinson Disease Questionnaire 39 (PDQ-39) or its shorter version (PDQ-8) in real life studies.^{11,12,13,16,17,18} However, little is known about the long-term effects of CSAI on HRQoL, as most studies involved a six month follow-up period.^{12,13,16,17} Only two studies had a longer follow-up period (12.5 (11.5) and 27.9 (24.9) months, respectively) but were limited by small cohort sizes and inconsistent findings.^{9,16} Furthermore, predictors of CSAI discontinuation were not addressed and remain largely unknown.^{19,20}

We conducted a retrospective analysis of a large series of consecutive advanced PD patients treated with CSAI over a 6-year period at the Salpêtrière Hospital in Paris and described their two-year follow-up. We focused on the evolution of HRQoL, motor fluctuations and dyskinesia two years after CSAI onset and attempted to identify predictors of CSAI discontinuation and HRQoL improvement.

RESULTS

Cohort's description

One-hundred and sixteen PD patients started CSAI treatment. Six patients were subsequently excluded from the analysis because they died during the study period (n = 4) or were lost to follow-up (n = 2). 110 patients were analyzed (Figure 1): 55 male patients, mean age 62.9 (9.6)

years, mean age at PD onset 50.9 (8.7) years, 47% with an akinetic-rigid motor subtype, mean PD duration 12 (6.1) years, median H&Y score off-state 3 and on-state 2, mean motor fluctuations duration 4.5 (3.6) years, mean ON UPDRS-III 19 (13) and mean UPDRS-IV 8.6 (3.5). Thirty-eight patients had a past history of impulse control disorders and 55 of depression (mean ASPBD 7.4 (4.3)). Of the 110 patients analyzed, 71 continued treatment up to the 24-month assessment and 39 patients discontinued the CSAI within the two years of follow-up. Table 1 shows the comparison of baseline characteristics between both groups.

Longitudinal follow-up

Quality of life and treatment satisfaction assessment

Of the 71 patients who continued treatment for 24 months, 14 patients were excluded from the analysis due to incomplete baseline and/or 24-month PDQ-39 assessment data (Figure 1). No difference in baseline characteristics was observed between patients excluded and patients analyzed. Of the 57 remaining patients, total PDQ-39 score at M24 was unchanged from M0 (42.34 at M0 vs 44.28 at M24, $p = 0.054$) with an effect size inferior to 0.2 (Table 2 and Figure 2). Post-hoc analysis demonstrated a trend towards significance present on the longitudinal analysis was not driven by a difference between M0 and M24. Stigma dimension showed the most significant improvement (34.96 at M0 vs 28.84 at M3, $p = 0.02$ and 30.83 at M24, $p = 0.018$). A significant improvement in mobility dimension was observed at M12 (57.68 at M0 vs 52.73 at M12, $p = 0.028$) but was no longer present at M24. Conversely, social support showed the largest significant deterioration (+55.8%) at M24. The communication dimension was also significantly altered at M24 (+19.6%). The remaining dimensions (activities of daily living, body discomfort, emotional well-being, cognitions) were unchanged.

Of the 57 patients, PDQ-39 improved from M0 to M24 in 26 patients, remained unchanged in one patient and deteriorated for the remaining (30 patients).

The satisfaction's self-questionnaire (Figure 3) reported an improvement (score between 0 and 2) on 5 items in more than 65% of the patients. Perceived improvement was maximal at M12 (motor fluctuations were improved in 91% of the patients, dyskinesias in 76% and quality of

life in 82%). At M24, motor fluctuations were reported to be improved in 84% of the patients, dyskinesias in 64% and quality of life in 79%. The device satisfaction's self-questionnaire showed a good general satisfaction (5.9 (2.3)), a moderate device's comfort (5.3 (2.4)), and it was evaluated as not particularly painful (2.3 (2.6)).

Motor and non-motor symptoms assessments

Table 3 shows the motor and non-motor assessment evolution with CSAI treatment. Fluc UPDRS sub-score improved by 32.4% at M24 ($p < 0.001$). Dysk UPDRS and UPDRS-III scores remained stable over the 24-months of follow-up ($p = 0.394$ and $p = 0.07$, respectively). ON UPDRS-II score showed a significant deterioration at 24-month follow-up ($p < 0.001$). However, such deterioration was not found for OFF UPDRS-II score ($p = 0.629$).

Regarding cognitive and non-motor status, at M24, we found a significant deterioration on UPDRS-I ($p < 0.001$), MMSE ($p = 0.041$) and FAB scale ($p = 0.003$). Conversely, total ASBPD did not significantly change ($p = 0.319$). In particular, there was no worsening of hyperdopaminergic behaviors.

Treatment adjustments

Treatment adjustments were analyzed in the group of patients who continued CSAI treatment over the two-year period. At baseline, the mean LEDD was 1298.3 (469.8) mg/day. Six patients had already been treated by DBS before CSAI onset. Most patients (71%) were treated with 24-hour continuous infusion from CSAI initiation and 15 patients (21%) received CSAI treatment only during daytime throughout the study. At M24, the mean daily dose of apomorphine was 93.9 (51.4) mg/day and the mean oral LEDD was 763.0 (418.9) mg/day; only two patients achieved complete withdrawal of oral antiparkinsonian medications (one of them had concomitant DBS). At baseline, 43% and 10% of patients received antidepressants and clozapine, respectively. At M24, 43% were taking antidepressants and 31% clozapine.

Adverse effects of CSAI

Prevalence of adverse effects related to CSAI was analyzed in patient group who continued CSAI treatment over the study period (Table 4). The most common adverse event was injection site skin nodules; its occurrence was stable throughout the study and reported by 53 to 57% of the patients. These nodules were not particularly painful and, on average, patients attributed 1 on the numerical pain rating scale. Digestive symptoms (nausea or vomiting) and orthostatic hypotension were particularly common during the first week of treatment (33.3% and 27.5% respectively). During follow-up, neuropsychiatric adverse events were reported in 20-30% of patients. Mild to moderate hallucinations were the most frequent and the rate of affected patients increased gradually during the 24 months of follow-up (18.6% of patients at M3 and 37.5% at M24). Mild impulse control disorders also occurred over time (27.9% at M3 vs 31.4% at M24). Other adverse-effects were daytime sleepiness or drowsiness (27 to 33% of patients), insomnia (11% to 18% of patients) and confusion (3 to 6% of patients). Patients mean weight remained stable during the study period (68.7 (16.9) kg at M3 and 67.9 (17.4) kg at M24).

Prediction of CSAI discontinuation

Thirty-nine patients (34%) discontinued CSAI before M24 (Figure 1) with a mean treatment duration of 7.4 (6.4) months. Reasons for discontinuation were: drug intolerance for 16 patients (severe psychosis or hallucinations (n = 7), impulse control disorders (n = 3), excessive somnolence (n = 2), severe skin reaction (n = 1), troublesome nausea (n = 1), device intolerance (n = 1), cognitive deterioration (n = 1)), incomplete or insufficient response for 15 patients (severe OFF persistence (n = 10) and troublesome dyskinesias (n = 5)), personal decision for 5 patients or programmed neurostimulation surgery for 3 patients. Six patients who stopped CSAI because of intolerance or poor efficiency switched to DBS.

The baseline characteristics (Table 1) of patients who stopped CSAI treatment (n = 39) were compared to patients who continued CSAI during at least two years (n = 71). They had a shorter duration of motor fluctuations ($p = 0.018$) and were more likely to have dyskinesias (p

= 0.049). They had a trend towards a shorter disease duration ($p = 0.060$), a worse OFF-state S&E score ($p = 0.059$), and a worse score on PDQ-39 body discomfort dimension (52.2 vs 46.0, $p = 0.072$).

A forward step-wise logistic regression analysis including 9 baseline factors (sex, disease duration, motor fluctuations duration, presence of dyskinesias, OFF-state S&E, Dysk UPDRS, Fluc UPDRS, ASBPD-1 and PDQ-39 body discomfort) revealed five different models for predicting treatment discontinuation (Table 5). Presence of dyskinesias (OR = 4.337, $p = 0.023$), higher ASBPD-1 score (OR = 1.285, $p = 0.016$), shorter disease duration (OR = 0.901, $p = 0.044$), male sex (OR = 0.306, $p = 0.034$) and worse OFF-state S&E (OR = 0.061, $p = 0.021$) were independent predictive factors of CSAI discontinuation. The model was a significant predictor of CSAI discontinuation ($\chi^2 = 25.23$, $p < 0.001$, Nagelkerke $R^2 = 0.350$).

Predictors of HRQoL improvement

We defined two groups of patients (Figure 1): patients with an improvement or stabilization on PDQ-39 at M24 ($n = 27$) and patients with a less favorable evolution on CSAI ($n = 69$) including patients who stopped CSAI ($n = 39$) or who worsened on PDQ-39 at M24 ($n = 30$).

The baseline characteristics of patients who had “improved” after 2 years of CSAI treatment compared to those patients with a less favorable evolution with CSAI were: higher OFF UPDRS-II (25 vs 20, $p = 0.031$) and worse total PDQ-39 (49 vs 40, $p = 0.001$). There were no significant differences with respect to age of PD onset, disease duration, Fluc and Dysk UPDRS, LEDD before patients received CSAI treatment or in non-motors symptoms (UPDRS-I, MMS, FAB, total ASBPD or past history of impulse control disorders).

The forward step-wise logistic regression model included 8 baseline factors (OFF-state H&Y, ON-state H&Y, OFF-state UPDRS-II, UPDRS-III, ASBPD-2, ASBPD-4, total PDQ-39, number of levodopa intakes per day). Only the baseline total PDQ-39 (OR = 1.052, 95% CI 1.010-

1.096, $p = 0.015$) was predictive of improved of HRQoL after two years of treatment. The model was a significant predictor of HRQoL improvement ($\chi^2 = 6.86$, $p = 0.009$, Nagelkerke $R^2 = 0.120$). Additionally, we found a significant positive correlation between baseline PDQ-39 and the improvement on PDQ-39 at M24 ($r = 0.37$, $p = 0.005$).

Patients aged over 80 years

In our study, the two oldest patients were two women aged 80 with a 3-4 years' history of motor fluctuations without dementia, who continued CSAI over the two-year follow-up. The first patient had an improvement in motor fluctuations but a deterioration of HRQoL, likely driven by worsening of non-motor symptoms. Cognition remained stable. For the second patient, motor fluctuations and non-motor symptoms were stable at M24 with an improvement of HRQoL. MMSE deteriorated from 28 to 24. The treatment was overall well tolerated in these two patients.

DISCUSSION

In a real-life study of 110 consecutive advanced PD patients treated with CSAI, 65% ($n = 71$) of the patients continued the treatment over the two-year period of follow-up. Of the 57 of 71 patients with sufficient data available we found HRQoL remained unchanged over this period. CSAI resulted in a sustained reduction of motor fluctuations whereas the benefit on dyskinesia was transient and mild. Patients had a positive self-evaluation of CSAI effect. The treatment was well-tolerated in most patients. Thirty-four per cent of the patients discontinued CSAI before achieving two years of treatment mainly due to poor tolerance (14%) or insufficient benefit (13%). The predictors of CSAI discontinuation were a lower OFF-state S&E, the presence of dyskinesias, a shorter disease duration, a poorer psychological status (ASBPd-1) and male sex. The only baseline predictor of a positive long-term effect of CSAI on HRQoL was a worse (higher) baseline PDQ-39 score: higher scores were associated with increased

improvement after 24 months. Our findings are important for clinical practice. They provide a large overview of what can be expected in advanced PD patients treated with CSAI in a routine care setting and clues to identify the patients who are more likely to benefit from this treatment.

This study has limitations related to its observational and retrospective design. Despite a larger initial population, there was a substantial amount of missing data. We excluded from the longitudinal analysis 20% of the patients due to incomplete data of PDQ-39 assessed at M0 or M24. For missing PDQ-39 data at M3, M6, M12 (around 2%), we applied validated statistical data replacement rules (NAO). Also, we did not assess non-motor symptoms with a dedicated scale, such as the Non-Motor Symptoms Scale (NMSS). Instead, we only used the UPDRS-I for this evaluation.

Real-life studies represent an important complementary approach to bridge the gap between efficacy demonstrated in RCT and effectiveness in everyday clinical practice. In routine care, we often deal with PD patients older than those included in RCT or patients who are suffering from comorbidities. We also have to consider long-term efficacy and tolerability as well as adherence rate and reasons for cessation of CSAI over time, which is rarely reported in randomized controlled studies. Our study provides important data on the effect of CSAI treatment on HRQoL in a real-life setting. One of the strengths of our work is the large sample size: only one short-term retrospective study had a similar large sample size¹⁶ while the two long-term retrospective studies had smaller samples.^{11,18} All patients were consecutively analyzed at fixed dates for 24 months and underwent a structured assessment designed to cover all major aspects of HRQoL, motor and non-motor symptoms. We also included a heterogeneous but realistic population of PD patients, especially regarding their age but also their neurosurgical expectative (patients already treated by DBS, waiting for DBS or switching to DBS).

HRQoL remained stable over a two-year period despite a sustained reduction in motor fluctuations. Furthermore, good treatment satisfaction was observed as assessed by a home-made satisfaction self-questionnaire, mainly focused on motor aspects. This paradox likely reflects the poor long-term effect of CSAI on non-motor manifestations in our patients. Indeed, non-motor symptoms represent a major determinant of HRQoL in PD patients and there is a close association between non-motor symptoms and HRQoL.^{21,22,23} Mood/apathy, sleep/fatigue, and miscellaneous domains of the NMSS score were the most significant factors for variance of PDQ-39 in a multicentre cross sectional study of 411 patients.²¹ Some patients with more limited alteration of HRQoL might have also ended up disappointed due to unrealistic expectations, which could have possibly resulted in worse PDQ-39 ratings. The natural disease progression in such patients with advanced PD with the appearance of levodopa-resistant motor and non-motor symptoms could also have influenced the observed long-term responsiveness. As a whole, the lack of HRQoL worsening over a two-year period could be interpreted as a positive effect of CSAI in this group of patients with advanced PD. Long-term data of CSAI effect on HRQoL is scarce. Previous reported studies have suggested a short-term positive effect of CSAI on HRQoL (Table 6). Four non-randomized, open-label studies found a significant improvement from 10 to 30% on HRQoL at six months.^{12,13,16,17} Only two studies focused on long-term HRQoL. Rambour et al¹⁸ with a follow-up of 27.9 (24.9) months did not find any difference on PDQ-39, while Martinez et al¹¹ compared CSAI versus conventional treatment over 12.5 (11.5) months and showed significant improvement on PDQ-8 within the CSAI group.

Baseline hyperdopaminergic behaviors were not different in patients who discontinued CSAI compared with patients who continued the treatment. Neuropsychiatric disorders, as assessed by the ASBPD, did not significantly worsen within the two-years of follow-up. When mild hallucinations and impulse controls disorders were reported, clozapine was prescribed during the study period. This allowed CSAI continuation in most patients. Our findings together with others published studies^{10,11,16} suggest an acceptable long-term behavioral tolerance profile of

CSAI. Clinicians may thus consider the use of CSAI even in patients with mild hyperdopaminergic behaviors on oral medication, taking into account the expected risk to benefit ratio.

Cognitive status showed a significant deterioration after twelve months of treatment in our study. A previous long-term follow-up study showed that cognitive worsening tends to occur after 15 months under treatment.⁹ The natural evolution of the disease likely accounts for this observation. Cognitive status was not a predictive factor of outcome in our models, possibly because the baseline cognitive status was overall relatively preserved in our patients.

PDQ-39 total score was the only baseline predictor of change in HRQoL after a 24-month treatment with CSAI in the multivariate model with a positive correlation between baseline PDQ-39 and long-term benefit on HRQoL. Patients with a poorer baseline HRQoL were more likely to improve their HRQoL. Improvement of HRQoL was independent of age, disease duration or severity of motor complications at baseline in our study. Despite low to moderate dyskinesia severity at baseline in our cohort, five patients stopped CSAI because of troublesome dyskinesia. Additionally, baseline dyskinesias predicted a higher risk for CSAI discontinuation and the benefit on dyskinesia seems only transient in most patients. Former studies showed that infusion therapies (CSAI and LCIG) can reduce significantly dyskinesias (particularly peak-dose), at least in some patients, but do not achieve a complete resolution.^{9,24,25,26} Although mechanisms involved in dyskinesias emergence, they are not fully understood: a combination of postsynaptic changes in dopamine receptor transmission and abnormal brain plasticity seems to occur and once established are probably irreversible.^{27,28}

Among the various sub-scores of PDQ-39, social support dimension deteriorated most over the two-year period. The use of CSAI would have required increased daily support from the families and friends.^{4,29} We hypothesize that some of the patients may not have received the expected support. The new constraints related to the use of CSAI and the therapeutic effect of

this treatment might also have altered the dynamic of the familial functioning.^{30,31} These various factors could have participated in a deterioration of the social sub-score.

Altogether, our findings suggest that the best candidates for CSAI in advanced fluctuating PD are patients: (i) with a poor baseline HRQoL, (ii) marked motor fluctuations, (iii) in whom dyskinesias are not the main complaint. Adequate support from the family and friends might also be critical.

Clinicians have three device assisted therapeutic option for advanced PD patients, namely CSAI, LCIG infusion and DBS.¹ In a real-life observational study, PD patients treated with CSAI, LCIG infusion or bilateral subthalamic DBS respectively had improved PDQ-8, UPDRS-IV and NMSS scores at 6 months.¹³ By contrast to our findings, improvements in HRQoL over 36 months was found after DBS³² or over 24 months after LCIG infusion.^{33,34} Patients included in these studies might have significantly differed from patients in our study, due to the application of more stringent eligibility criteria. Unfortunately, no study directly compares the long-term effect of all three options. Tailoring individual therapy for the individual patient is based on limited evidence regarding individualized efficacy and tolerability. In the absence of a comparative study, therapeutic choice remains challenging.²⁹

METHODS

We retrospectively collected data from consecutive PD patients, who have been treated with CSAI at the Salpêtrière University hospital (Paris) over a 6-year period and described their two-year follow-up. All patients fulfilled the Movement Disorder Society Clinical Diagnostic Criteria for PD.³⁵ CSAI introduction was decided in routine care after medical evaluation and patient informed agreement.

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by a local ethics committee (CPP Ile de France 6, Paris). The study was classified as an observational study (class of evidence IV) and the data

collection was then approved by the national commission for data protection (CNIL) according to the French regulation rules. Patients have been informed that their medical charts could be used for research purpose after anonymization of the data. No written consent was required by the ethics committee.

Treatments procedures

Patients started CSAI treatment during a two-week hospital stay (baseline = M0). The initial dose was 0.5-1 mg/h and then gradually increased until the best clinical response was obtained during this hospitalization. The oral and/or transdermal anti-parkinsonian treatments were gradually reduced as tolerated (prioritizing dopamine agonist's reduction). In the absence of contraindications, domperidone treatment was prescribed in patients with digestive intolerance to apomorphine. Targeted therapeutic education to prevent all adverse events, especially subcutaneous nodules, was provided.

Patients were re-admitted for five days at 3 (M3), 6 (M6), 12 (M12) and 24 (M24) months after CSAI initiation to assess quality of life, efficacy and tolerance of the treatment. During this two-year period, the clinical teams performed therapeutic adaptations as part of routine care to optimize clinical response.

Clinical assessments

Demographic data (age, sex), age at PD onset, disease duration, PD motor subtype (akinetic-rigid type versus tremor-dominant type), duration of motor fluctuations (period, in years, between the first appearance of motor fluctuations and the date of assessment) and presence of dyskinesias at inclusion were collected at baseline. All treatments, classified as parkinsonian, non-parkinsonian and neurosurgical treatments were recorded. Levodopa equivalent daily doses (LEDD) were computed.³⁶

Evaluations were performed at all visits (M0, M3, M6, M12, M24). Quality of life was evaluated by PDQ-39 (range 0 to 100).³⁷ This scale was subdivided in two sub-scores: physical (including

mobility, activities of daily living and bodily discomfort dimensions) and psychological (corresponding to emotional well-being, stigma, social support, cognition and communication dimensions). Motor status was assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS)³⁸ part II (UPDRS-II, OFF and ON conditions, range 0 to 52), part III (UPDRS-III quantified in ON state, range 0 to 108) and part IV (UPDRS-IV, range 0 to 23); the Hoehn and Yahr scale (H&Y, OFF and ON conditions, range 0 to 5)³⁹ and the Schwab and England Activities of Daily Living Scale (S&E, OFF and ON conditions, range 0 to 100%)⁴⁰. We defined two sub-scores based on UPDRS-IV: Dysk UPDRS corresponding to dyskinesias assessment (items 32 to 35 of UPDRS-IV, range 0 to 13) and Fluc UPDRS corresponding to motor fluctuations assessment (items 36 to 39 of UPDRS-IV, range 0 to 7). Non-motor and cognitive status were assessed with UPDRS part I (UPDRS-I, range 0 to 16), Mini Mental State Examination score (MMSE, range 0 to 30)⁴¹ and Frontal Assessment Battery (FAB, range 0 to 18)⁴². The Ardouin Scale of Behavior in Parkinson's Disease (ASBPD, range 0 to 84)⁴³ was used to track changes in mood and behavior related to dopaminergic medication with ASBPD-1 quantifying the general psychological state, ASBPD-2 the overall functioning in apathetic mode, ASBPD-3 the non-motor fluctuations, and ASBPD-4 the hyperdopaminergic behaviors.

At each follow-up visit (M3, M6, M12, M24), we applied a treatment satisfaction's self-questionnaire containing 5 items (motor fluctuations, dyskinesias, gait disturbances, swallowing and quality of life) rated from zero (strong improvement) to four (strong worsening) and a 3-items visual analog scale (range 0 to 10) indicating the level of pain, the device's comfort and general satisfaction with the CSAI, respectively.

Antiparkinsonian treatments (oral, transdermal and CSAI treatments) and their adverse effects were collected at each visit; a numerical rating scale was used to quantify the nodule's pain (range 0 to 10; with 0 indicating no pain). For patients who stopped CSAI before the 2-year follow-up visit, time and cause for discontinuation were also collected.

Objectives

The primary objective was to determine the change in HRQoL of PD patients, as measured by the PDQ-39 scale, at the two-year follow-up. The secondary objectives were to evaluate the change in motor (UPDRS-II, UPDRS-III, UPDRS-IV, Dysk UPDRS, Fluc UPDRS, H&Y, S&E, treatment satisfaction's self-questionnaire), non-motor (UPDRS-I) and cognitive (MMSE, FAB, ASBPD) status during the two-years CSAI treatment. Safety assessment included evaluation of adverse events and local tolerability. We then focused on the predictive factors of early CSAI dropout or HRQoL improvement.

Statistical analysis

Data analysis was conducted with R (3.6.0) system. The normality of the distribution of the data was assessed by the Shapiro-Wilk test and the homogeneity of the variance by the Levene test. Variables that failed the Shapiro-Wilk or the Levene test were analyzed with nonparametric statistics. Parametric descriptive statistics were used to describe clinical characteristics of the cohort and to detect the presence of outliers.

For baseline data, we performed a comparative analysis between patients who discontinued the treatment and patients with 24 months of follow-up. Categorical variables were analyzed using Pearson's χ^2 test or Fisher's exact test and quantitative variables with Student's t-test, if normally distributed, or the Mann-Whitney's test, if they were non-parametric.

For the longitudinal analysis, quantitative missing data at M3, M6, M12 were inputted using the Nearest Available Observation (NAO). NAO sets the missing data as equal to the distance-weighted time mean⁴⁴ of the closest available data in time (backward and forward) for each patient. Then we compared patient's evolution at time points from M0 to M24 using a repeated measures related-samples Friedman's two-way analysis of variance by ranks test followed by Mann-Whitney post-hoc tests with a Bonferroni Correction applied for multiple comparison. Normally distributed variables were analyzed by repeated measure ANOVA followed by the Bonferroni post-hoc test for multiple comparisons. Categorical variables were compared using

McNemar-Bowker Test of Symmetry. A *p* value of less than 0.05 was defined as significant. Results will be presented as the mean (standard deviation, SD), unless otherwise stated.

In order to identify the clinical baseline predictors of treatment evolution we performed two multiple logistic regressions (MLR) using stepwise forward elimination. A first MLR was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for predicting treatment discontinuation and relevant clinical determinants. Patients who discontinued CSAI and patients who continued treatment during the 24-month follow-up defined the categorical dependent variable. A second MLR was used to estimate ORs and 95% CI for predicting the HRQoL improvement with CSAI therapy and relevant clinical determinants. Improved patients (patients with improved or stabilized PDQ-39 at M24 - relative change compared to baseline \leq 0%) and patients with a less favorable evolution (patients who stopped CSAI or worsened on PDQ-39 at M24 - relative change $>$ 0%) defined the categorical dependent variable. Variables with a *p* $<$ 0.2 in the univariate analysis were included in the multiple Wald test using stepwise forward elimination in both MLR. The relation between baseline PDQ-39 and PDQ-39 change between M0 and M24 was investigated with the Pearson method.

DATA AVAILABILITY

All data is available at the Department of Neurology of the Salpêtrière Hospital (Paris, France). The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ACKNOWLEDGEMENTS

The study was supported by the Société Française de Médecine Esthétique (SFME).

AUTHOR CONTRIBUTIONS

B.M., E.C., E.H. and E.R. designed and conceptualized the study.

B.M., B.D., E.C., E.B., C.V.F., P.D., A.M., L.L.M., C.D., F.C.D., D.B., N.V., C.T., L.M., H.L., C.L., E.M., Y.W., D.G. and M.V. contributed to data collection.

M.D. conducted statistical analysis of data.

B.M., E.C., M.D, E.H. and E.R. contributed to the interpretation of data.

B.M., E.C., E.H. and E.R. contributed to writing manuscript.

B.M., B.D., E.C., M.D., E.B., C.V.F., P.D., A.M., L.L.M., C.D., F.C.D., D.B., N.V., C.T., L.M., H.L., C.L., E.M., Y.W., D.G., M.V., E.H., E.R. contributed to critical revision of the manuscript for intellectual content and final approval of the completed version.

COMPETING INTERESTS

B.D. served on scientific advisory boards for Aguettant, received research support from Orkyn, Elivie, received travel grant from Orkyn, Elivie;

E.B. received travel grant from Vitalaire and PEPS;

C.V.F. received a grant from Association Nationale de la Recherche et de la Technologie (A.N.R.T.), full-time employment by Air Liquide Healthcare;

P.D. received a travel grant from UCB pharma;

A.M. received travel funding from Abbvie and Merz;

L.L.M. received speech honoraria from Lundbeck, Teva, received travel funding from the Medtronic, Teva and AbbVie;

C.D. received travel grant from Medtronic and Boston Scientific;

D.B. received travel grant from Boston Scientific;

L.M. received a travel grant from Orkyn (Air Liquide), Abbvie, Elivie, Medtronic;

H.L. received a travel grant from Orkyn (Air Liquide), Abbvie, Elivie;

E.M. received travel grant from Elivie;

D.G. served on scientific advisory boards for AbbVie and Zambon; received speech honoraria from Medtronic, Abbvie; received research support from Air Liquide; received travel grant from Abbvie;

E.H. served on scientific advisory boards for Medtronic and Boston Sci, received honoraria for speeches from Boston Sci, received travel grant from Merz;

E.R. served on scientific advisory boards for Orkyn, Aguettant, received honoraria for speeches from Orkyn, Aguettant, Everpharma, received research support from Orkyn, Aguettant, Elivie, Everpharma, received travel grant from Vitalaire, PEPS development,

Aguettant, Orkyn, Elivie, Adelia Medical.

B.M, E.C., M.D., F.C.D., N.V, C.T., C.L., Y.W. and M.V. declare absence of commercial or financial relationships that could be construed as potential conflicts of interest.

ADDITIONAL INFORMATION

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There is no supplementary data.

FIGURES

Figure 1: Flow chart of the study

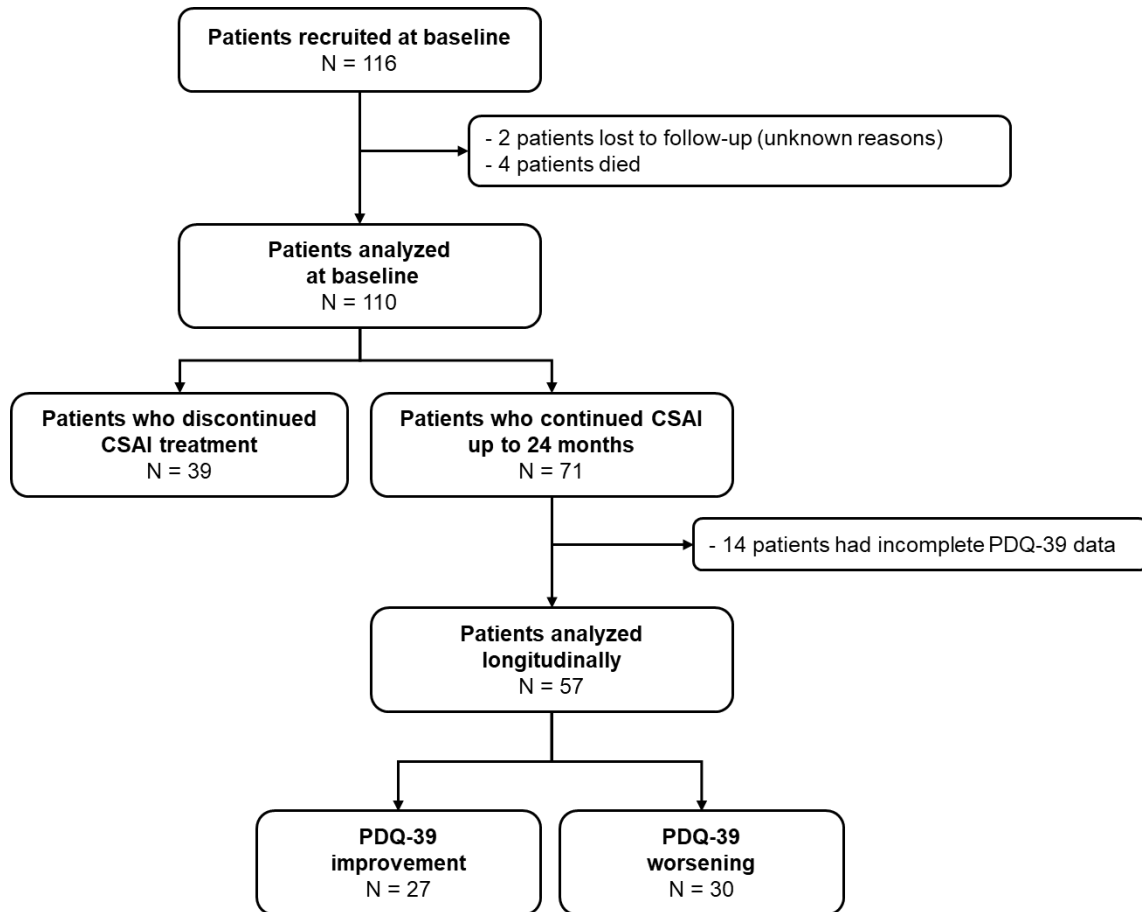


Figure 2: Comparison of HRQoL measured by PDQ-39.

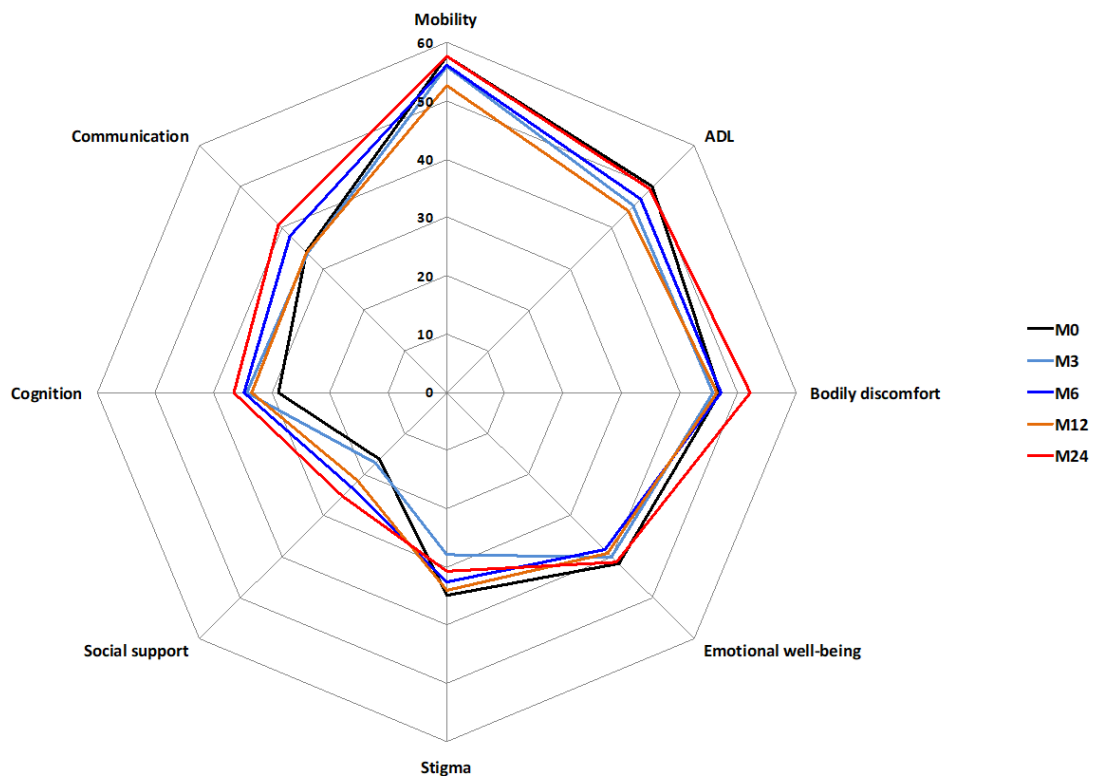
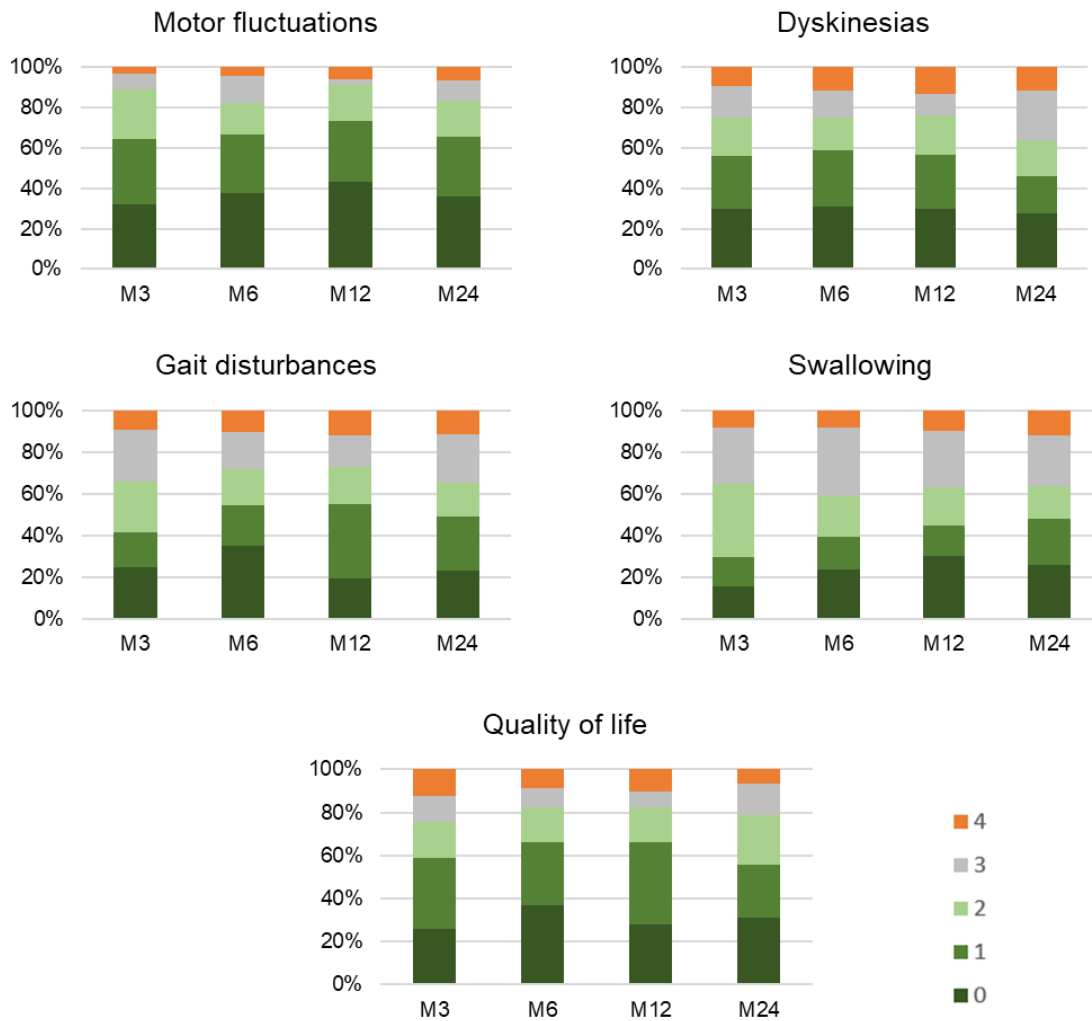


Figure illustrates the evolution of each dimension of PDQ-39 at baseline (M0) and at each follow-up visit (M3, M6, M12, M24).

Figure 3: Satisfaction self-assessment questionnaire



Histograms illustrating the proportion of patients for each score on the 5 items of the treatment satisfaction self-questionnaire. Motor fluctuations was the item with the largest percentage of patients stating improvement (83 to 91%). Quality of life was improved in 76 to 82% of patients and dyskinesias in 64-76%. Gait and swallowing disturbances showed a more modest percentage (60-73%).

0=very improved, 1=moderately improved, 2=little improved, 3=not improved, 4=deteriorated

TABLES

Table 1 Baseline characteristics.

	Continued CSAI Therapy (n = 71)	Discontinued CSAI Therapy (n = 39)	p-value
Demographics			
Male	32 (45)	23 (59)	0.163 ^a
Age, years	63 (9.7)	62 (9.6)	0.342 ^b
PD characteristics			
Age at PD onset, years	51 (9)	51 (8.2)	0.938 ^b
Disease duration, years	13 (5.9)	11 (6.4)	0.0607 ^c
Motor fluctuations duration, years	5.1 (3.8)	3.5 (3)	0.0184^c
Dyskinesias, yes	42 (60)	27 (79)	0.0494^a
Motor status			
UPDRS-II ON	8.6 (7.6)	9.1 (7.7)	0.644 ^c
UPDRS-II OFF	22 (9.2)	21 (8.5)	0.505 ^c
UPDRS-III ON	19 (13)	17 (12)	0.507 ^c
UPDRS-IV total	8.1 (3.5)	9.3 (3.6)	0.101 ^b
Dysk UPDRS	3.6 (2.9)	4.2 (2.7)	0.172 ^c
Fluc UPDRS	3.5 (1.5)	3.9 (1.3)	0.186 ^c
Hoehn & Yahr OFF	3.1 (1.1)	3.2 (1.1)	0.791 ^c
Schwab & England OFF	55 (24)	47 (21)	0.0594 ^c
Cognitive Status			
MMSE	27 (3)	27 (3.5)	0.346 ^c
FAB	16 (2.6)	15 (2.9)	0.71 ^c
UPDRS-I	2.9 (2)	3.2 (2.1)	0.681 ^c
ASBPD total	8.1 (4.6)	7.1 (4.3)	0.265 ^c
ASBPD-1	2.9 (2.2)	3.9 (3)	0.115 ^c
ASBPD-2	0.50 (0.8)	0.49 (0.8)	0.754 ^c

ASBPD-3	1.3 (1.3)	1.4 (1.3)	0.462 ^c
ASBPD-4	2.4 (2.5)	2.2 (1.1)	0.733 ^c
PDQ-39 total score	42.6 (12.5)	43.1 (14.4)	0.870 ^b
PD treatment history			
Total LEDD, mg	1299 (461)	1378 (665)	0.956 ^c
Dopamine agonists, LEDD, mg	130 (132)	150 (229)	0.848 ^c
Amantadine	26 (37)	11 (28)	0.372 ^a
Clozapine	7 (10)	2 (5)	0.695 ^a
Antidepressants	29 (41)	17 (45)	0.451 ^a

Values are mean (SD) or n (%).

^aPearson's χ^2 test ; ^bStudent's t-test ; ^cMann-Whitney test

Abbreviations: CSAI = Continuous subcutaneous apomorphine infusion; PD = Parkinson Disease; UPDRS = Unified Parkinson's Disease Rating Scale; UPDRS-I = UPDRS part I, Mentation, Behavior and Mood; UPDRS-II = UPDRS part II, Activities of Daily Living; UPDRS-III = UPDRS part III, Motor Examination; UPDRS-IV = UPDRS part IV, Complications of Therapy; Dysk UPDRS = items 32 to 35 of UPDRS-IV; Fluc UPDRS = items 36 to 39 of UPDRS-IV; MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; ASBPD-1 = ASBPD part 1, general psychological state; ASBPD-2 = ASBPD part 2, overall functioning in apathetic mode; ASBPD-3 = ASBPD part 3, non-motor fluctuations; ASBPD-4 = ASBPD part 4, hyperdopaminergic behaviors; PDQ-39 = Parkinson Disease Questionnaire 39; LEDD = Levodopa equivalent daily dose.

Table 2 Assessment of patient's quality of life measured by PDQ-39 (n=57). Changes for each dimension, physical or psychological sub-scores and PDQ-39 total score.

Dimension	M0	M3	M6	M12	M24	Friedman test p-value	Relative Change M0-M24
Physical score	53.5 (18.1)	51.3 (18.3)	51.9 (17.6)	48.9 (17.5) ^a	54.1 (17.0)	0.013	+ 1.2%
Mobility	57.7 (22.7)	56.0 (22.5)	56.2 (20.6)	52.7 (19.9) ^a	57.6 (18.8)	0.036	- 0.09%
ADL	49.9 (20.3)	45.2 (20.0)	47.0 (20.6)	44.0 (20.4)	49.3 (22.7)	0.134	- 1%
Bodily discomfort	46.9 (20.6)	45.7 (19.7)	47.1 (21.2)	46.4 (20.1)	52.1 (19.6)	0.297	+ 11%
Psychological score	32.8 (11.5)	32.0 (13.4)	34.3 (12.6)	33.3 (13.6)	35.6 (12.4)	0.366	+ 8%
EMO	41.7 (19.0)	40.1 (17.6)	38.3 (16.2)	39.0 (17.5)	41.2 (15.8)	0.871	- 1.4%
Stigma	35.0 (20.3)	28.0 (21.9) ^a	32.6 (25.8)	34.1 (23.1) ^a	30.8 (22.9) ^a	0.027	- 11.8%
Social support	16.2 (17.8)	17.3 (21.2)	23.1 (23.7)	21.5 (21.6)	25.3 (21.9) ^a	0.015	+ 55.8%
Cognition	28.8 (17.7)	34.2 (22.0)	34.8 (17.8)	33.5 (18.3)	36.4 (18.4)	0.387	+ 26%
Communication	34.1 (19.5)	33.8 (22.2)	38.0 (22.2)	33.9 (19.2)	40.8 (19.6) ^a	0.018	+ 19.6%
PDQ-39 total	42.3 (12.3)	40.8 (13.7)	42.9 (14.8)	40.3 (14.0)	44.3 (13.4)	0.054	+ 4.6%

Data are mean (SD). The PDQ-39 range is 0–100; the higher the score, the worse the self-reported quality of life; negative change = improvement. Missing values in PDQ-39 domain scores were imputed using the nearest available observations. Related-samples Friedman's two-way analysis of variance by ranks test followed by Wilcoxon tests with a Bonferroni Correction applied. ^ap-value < 0.05 compared to M0. Since there was a strong trend towards significance for PDQ-39 total (p = 0.054), we checked the score evolution compared to M0 by paired comparisons and found that all the p-values were > 0.23); Relative change = (mean Test_{follow-up} – mean Test_{baseline})/Test_{baseline} x 100.

Abbreviations: PDQ-39= 39-item Parkinson's disease questionnaire; ADL = Activities of daily living; EMO = Emotional well-being.

Table 3 Changes in motor, non-motor and cognitive dimensions with CSAI treatment (n = 57)

	M0	M3	M6	M12	M24	Friedman test p-value
Motor Status						
UPDRS-II ON	7.9 (6.6)	8.3 (5.8)	8.6 (7.2)	9.1 (6.8)	12.0 (8.6) ^c	0.002
UPDRS-II OFF	22.2 (9.1)	20.8 (8.0)	20.4 (7.7)	20.5 (7.8)	21.8 (9.7)	0.629
UPDRS-III ON	18.5 (11.1)	16.8 (13.2)	18.7 (13.4)	18.8 (13.6)	22.3 (14.1)	0.07
UPDRS-IV	8.1 (3.0)	7.2 (3.6)	7.2 (3.6)	7.4 (3.7)	8.0 (3.9)	0.960
Dysk UPDRS	3.4 (2.7)	3.0 (2.5)	3.4 (3.0)	3.4 (2.7)	3.9 (2.7)	0.394
Fluc UPDRS	3.7 (1.4)	2.9 (1.4) ^b	2.7 (1.5) ^a	2.6 (1.6) ^b	2.5 (1.6) ^c	< 0.001
H&Y OFF	3.0 (1.1)	3.1 (1.2)	3.0 (1.1)	3.0 (1.0)	3.3 (1.1)	0.264
S&E OFF	60 (20)	60 (20)	60 (20)	60 (20)	50 (30)	0.422
Cognitive/Non-motor status						
UPDRS I	3.0 (1.8)	2.6 (2.0)	2.5 (2.0)	3.0 (2.6)	4.0 (2.7) ^b	< 0.001
MMSE	27.4 (3.1)	26.7 (3.5)	27.1 (3.4)	27.4 (3.8)	26.5 (4.1)	0.041
FAB	15.7 (2.6)	15.4 (2.9)	15.9 (2.4)	15.7 (2.5)	14.9 (3.2) ^b	0.003
ASBPD total score	6.6 (4.4)	6.4 (4.5)	6.5 (4.1)	6.4 (4.1)	7.0 (3.7)	0.319
ASBPD-1	2.6 (2.1)	3.0 (2.6)	3.0 (2.5)	3.1 (2.3)	3.5 (2.5)	0.106
ASBPD-2	0.5 (0.7)	0.4 (0.7)	0.2 (0.5)	0.2 (0.5)	0.6 (0.9)	0.019
ASBPD-3	1.4 (1.3)	0.9 (1.0)	1.0 (1.0)	1.0 (1.1)	0.8 (0.9)	0.06
ASBPD-4	2.3 (2.6)	2.1 (2.1)	2.1 (1.8)	2.2 (2.3)	2.2 (1.8)	0.778

Values presented are mean (SD). Post-hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied. ^ap-value < 0.05, ^bp-value < 0.01, ^cp-value < 0.001 compared to M0 by Wilcoxon signed-rank test.

Abbreviations: CSAI = Continuous subcutaneous apomorphine infusion; PD = Parkinson Disease; UPDRS = Unified Parkinson's Disease Rating Scale; UPDRS-I = UPDRS part I, Mentation, Behavior and Mood; UPDRS-II = UPDRS part II, Activities of Daily Living; UPDRS-III = UPDRS part III, Motor Examination; UPDRS-IV = UPDRS part IV, Complications of Therapy; Dysk UPDRS = items 32 to 35 of UPDRS-IV; Fluc UPDRS = items 36 to 39 of UPDRS-IV; H&Y = Hoehn and Yahr scale; S&E = Schwab and England Activities of Daily Living Scale; MMSE = Mini Mental State Examination score; FAB = Frontal Assessment Battery; ASBPD = Ardouin Scale of Behavior in Parkinson's Disease; ASBPD-1 = ASBPD part 1, general psychological state; ASBPD-2 = ASBPD part 2, overall functioning in apathetic mode; ASBPD-3 = ASBPD part 3, non-motor fluctuations; ASBPD-4 = ASBPD part 4, hyperdopaminergic behaviors.

Table 4 Prevalence of adverse effects in percentage.

	M3	M6	M12	M24
Skin nodules	52.9	54.9	61.4	57.4
Confusion	5.8	2.8	2.9	2.9
Hallucinations	18.6	19.4	27.1	37.5
ICD^a	31.4	26.4	32.9	27.9
Sedation/Drowsiness	33.3	30.6	30.0	26.5
Insomnia	14.5	18.1	21.4	11.8
Nausea	30.4	23.6	20.0	11.8
Orthostatic hypotension	23.2	22.9	24.3	31.3
Symptomatic Orthostatic hypotension	10.1	8.3	7.1	9.1

Values are in percentage (%).

^aFrom minimal to moderate impulse control disorders (ICD) such as hypersexuality, compulsive eating, pathological gambling, punding, hobbyism.

Table 5 Stepwise logistic regression analysis for variables predicting treatment discontinuation.

	Variables	β	S.E.	p-value	OR (95% CI)
Model 1	S&E OFF	-2.496	1.028	0.015	0.082 (0.011-0.618)
Model 2	S&E OFF	-2.36	1.057	0.026	0.094 (0.012-0.75)
	ASBPD 1	0.207	0.096	0.032	1.229 (1.018-1.484)
Model 3	S&E OFF	-2.656	1.105	0.016	0.07 (0.008-0.613)
	ASBPD-1	0.206	0.098	0.036	1.229 (1.013-1.49)
	Sex	-1.026	0.516	0.047	0.358 (0.13-0.986)
Model 4	S&E OFF	-2.383	1.135	0.036	0.092 (0.01-0.854)
	ASBPD-1	0.242	0.103	0.018	1.274 (1.042-1.558)
	Sex	-1.209	0.541	0.025	0.298 (0.103-0.862)
	Dyskinesias	1.28	0.613	0.037	3.597 (1.081-11.969)
Model 5	S&E OFF	-2.79	1.207	0.021	0.061 (0.006-0.654)
	ASBPD-1	0.25	0.104	0.016	1.285 (1.048-1.575)
	Sex	-1.183	0.557	0.034	0.306 (0.103-0.913)
	Dyskinesias	1.467	0.645	0.023	4.337 (1.224-15.368)
	Disease duration	-0.105	0.052	0.044	0.901 (0.813-0.997)

Abbreviations: S&E = Schwab and England Activities of Daily Living Scale; ASBPD-1 = Ardouin Scale of Behavior in Parkinson's Disease, part 1, general psychological state.

Table 6 Data from previous studies that evaluated the effect of CSAI on HRQoL.

Study/year Study design	N	Age at CSAI onset	Follow- up period (months)	PDQ applied	PDQ baseline	PDQ follow-up	Results p-values
Naidu et al. 2009 Observational	17	62 (14)	6	PDQ-8	NA	NA	Significant improvement
Martinez-Martin et al. 2011 Observational	17 ^a	59.5 (11.7)	12.5 (11.5)	PDQ-8	55.70	32.35	Relative change = - 41.9%, $p = 0.001$
Rambour et al. 2014 Retrospective	27	63,1 (9,3)	27.9 (24.9)	PDQ-39	71	77	No changes on quality of life, $p =$ 0.4843
Martinez-Martin et al. 2015 Prospective	43 ^b	62.3 (10.6)	6	PDQ-8	49.85 (16.59)	35.03 (18.00)	Relative change = - 29.75%, $p < 0.0001$
Drapier et al. 2016 Prospective	100	66.7 (10.8)	6	PDQ-39	41.2 (15.5)	36.5 (13.9)	Relative change = - 11.3%, $p = 0.0114$; Significant improvements on the BD, stigma, mobility and EMO
Auffret, et al. 2016 Observational	12	66.7 (10.8)	6	PDQ-39	33.8 (17.7)	29.6 (14.3)	Trends toward improvement on total PDQ-39 ($p =$ 0.08), ADL ($p =$

							0.08), bodily discomfort ($p = 0.09$)
Katzenschlager, et al. 2018 RCT	53 ^c	63.6 (9.3)	12 weeks	PDQ-8	32.67	32.61	No changes on quality of life.
Dafsari et al. 2019 Prospective	39	62.3 (10.6)	6	PDQ-8	43.1	30.3	Relative change = - 30.3%, $p < 0.001$

Values presented are mean (SD).

^aCSAI treated group was compared with an untreated group (n=17). During follow-up, the control group showed a worsening on PDQ-8 while CSAI group showed a highly significant improvement.

^bThe study compared 43 patients on CSAI and 44 on LCIG. Difference between groups on PDQ-8 was not statistically significant.

^cTOLEDO study. Change on PDQ-8 was not significantly different compared with placebo, mean difference -2.47 (95% CI -7.62 to 2.69, $p=0.3971$).

Abbreviations: BD = Bodily discomfort; ADL = Activities of daily living; EMO = Emotional well-being

II. Analysis of treatment trajectories as a function of Parkinson's disease symptoms

Data are given as Median [1st quartile, 3rd quartile] for continuous variables and as count (percentages) for categorical variables. The significantly different classes are marked by the letter of the class. Class 1 is noted as a, Class 2 as b, Class 3 as c, Class 4 as d, and Class 5 as e. * $p < 0.05$

Supplementary Table 1: Characteristics of patients assigned to the classes of %apo trajectories

var	N	all	Class 1 (a)	Class 2 (b)	Class 3 (c)	Class 4 (d)	Class (e)	p
Count		120	22 (18.33%)	17 (14.17%)	25 (20.83%)	44 (36.67%)	4 (3.33%)	
Gender (F)	120	60 (50.00%)	12 (54.55%)	7 (41.18%)	15 (60.00%)	20 (45.45%)	2 (50.00%)	0.716
Age at Baseline	120	64.00 [56.75, 69.00]	59.00 [53.75, 64.25]	62.00 [60.00, 69.00]	64.00 [58.00, 70.00]	67.00 [56.50, 72.00]	61.50 [59.75, 63.50]	0.227
PD Duration	120	11.00 [8.00, 15.00]	7.00 [4.50, 9.75] b, c, d	12.00 [10.00, 14.00] a	13.00 [10.00, 17.00] a	11.50 [8.00, 14.25] a	15.50 [12.75, 17.25]	0.003*
UPDRS part I	109	2.00 [2.00, 4.00]	2.00 [1.00, 4.00]	3.00 [2.00, 4.00]	2.00 [1.50, 3.00]	3.00 [2.00, 4.00]	3.50 [1.50, 5.25]	0.392
UPDRS part II in ON	107	7.00 [3.00, 12.00]	5.00 [2.00, 10.00]	6.00 [2.75, 11.25]	8.00 [3.00, 11.00]	8.00 [5.00, 14.00]	14.50 [11.75, 18.75]	0.116
UPDRS part II in OFF	106	22.00 [15.00, 26.00]	20.50 [16.75, 24.00]	22.50 [18.00, 28.75]	21.00 [16.00, 25.00]	22.00 [15.00, 28.00]	22.50 [14.75, 30.50]	0.798
UPDRS part III in ON	107	17.00 [10.50, 25.00]	13.00 [10.00, 18.00]	20.00 [14.00, 26.00]	17.00 [8.00, 21.00]	17.00 [12.00, 27.25]	23.00 [19.25, 29.50]	0.120
UPDRS part IV	108	8.00 [6.00, 10.00]	9.00 [7.00, 11.00]	8.00 [7.00, 10.00]	8.00 [6.00, 10.00]	8.00 [5.00, 9.00]	11.00 [8.75, 12.25]	0.505
HY in ON	101	2.00 [1.50, 2.50]	2.00 [1.38, 2.50]	2.00 [2.00, 2.75]	2.00 [1.38, 2.50]	2.00 [1.50, 3.00]	2.50 [1.88, 3.25]	0.819
HY in OFF	98	3.00 [2.50, 4.00]	3.00 [2.00, 4.00]	3.00 [2.75, 4.00]	3.00 [2.50, 4.00]	3.00 [2.50, 4.00]	4.00 [3.75, 4.25]	0.375
SE in ON	103	0.80 [0.70, 0.90]	0.90 [0.80, 0.90]	0.80 [0.75, 0.90]	0.90 [0.70, 0.90]	0.80 [0.80, 0.90]	0.70 [0.62, 0.72]	0.217
SE in OFF	98	0.60 [0.40, 0.70]	0.60 [0.48, 0.72]	0.60 [0.52, 0.70]	0.55 [0.40, 0.72]	0.60 [0.38, 0.70]	0.40 [0.38, 0.45]	0.742
MMSE	109	28.00 [25.00, 29.00]	29.00 [26.00, 29.00]	26.00 [23.75, 29.00]	28.00 [25.00, 30.00]	28.00 [25.50, 29.00]	28.00 [25.50, 30.00]	0.403
FAB	109	17.00 [15.00, 18.00]	18.00 [17.00, 18.00] b, d	15.50 [12.75, 17.00] a	17.00 [15.00, 18.00]	17.00 [13.50, 17.00] a	16.50 [15.50, 17.00]	0.014*
PDQ-39	104	43.59 [33.97, 51.28]	41.99 [31.73, 49.36]	41.67 [32.69, 48.72]	44.87 [40.06, 53.21]	41.03 [33.97, 47.44]	55.77 [49.84, 60.26]	0.155
ASBPD part II	109	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	1.50 [0.75, 2.25]	0.133
ASBPD	109	7.00 [4.00, 10.00]	8.00 [4.00, 12.00]	7.50 [4.75, 10.25]	6.00 [4.00, 10.00]	7.00 [4.00, 10.00]	5.50 [3.75, 8.75]	0.918

Supplementary Table 2: Characteristics of patients assigned to the classes of %apo night trajectories

var	N	all	Class 1 (a)	Class 2 (b)	Class 3 (c)	Class 4 (d)	Class (e)	p
Count		120	41 (34.17%)	42 (35%)	3 (2.5%)	25 (20.83%)	1 (0.83%)	
Gender (F)	120	60 (50.00%)	24 (58.54%)	18 (42.86%)	1 (33.33%)	13 (52.00%)	0 (0.00%)	0.530
Age at Baseline	120	64.00 [56.75, 69.00]	63.00 [57.00, 68.00]	65.00 [57.25, 69.75]	62.00 [57.00, 67.00]	62.00 [56.00, 70.00]	70.00 [70.00, 70.00]	0.929
PD Duration	120	11.00 [8.00, 15.00]	13.00 [10.00, 16.00]	11.00 [7.00, 13.75]	9.00 [6.50, 10.50]	9.00 [8.00, 12.00]	15.00 [15.00, 15.00]	0.131
UPDRS part I	109	2.00 [2.00, 4.00]	2.00 [2.00, 5.00]	2.50 [2.00, 4.00]	3.00 [2.50, 4.50]	2.00 [2.00, 4.00]	1.00 [1.00, 1.00]	0.697
UPDRS part II in ON	107	7.00 [3.00, 12.00]	8.00 [5.50, 12.25]	8.00 [3.25, 11.00]	5.00 [2.50, 9.00]	5.00 [2.00, 13.00]	3.50 [3.50, 3.50]	0.643
UPDRS part II in OFF	106	22.00 [15.00, 26.00]	22.00 [15.00, 26.50]	21.00 [15.50, 25.00]	19.00 [12.00, 23.50]	22.50 [19.50, 26.50]	21.00 [21.00, 21.00]	0.902
UPDRS part III in ON	107	17.00 [10.50, 25.00]	17.00 [12.75, 26.25]	17.50 [12.00, 22.25]	26.00 [14.50, 29.00]	13.00 [9.00, 19.50]	9.00 [9.00, 9.00]	0.501
UPDRS part IV	108	8.00 [6.00, 10.00]	9.00 [6.75, 11.00]	8.00 [6.00, 10.00]	9.00 [7.50, 10.00]	7.00 [6.00, 9.00]	8.00 [8.00, 8.00]	0.407
HY in ON	101	2.00 [1.50, 2.50]	2.00 [1.25, 3.00]	2.00 [1.38, 2.50]	1.50 [1.25, 1.75]	2.00 [2.00, 2.50]	0.00 [0.00, 0.00]	0.337
HY in OFF	98	3.00 [2.50, 4.00]	3.00 [2.50, 4.00]	3.00 [2.50, 4.00]	3.00 [2.50, 3.50]	3.50 [2.50, 4.88]	3.00 [3.00, 3.00]	0.589
SE in ON	103	0.80 [0.70, 0.90]	0.80 [0.70, 0.90]	0.90 [0.74, 0.90]	0.95 [0.92, 0.98]	0.85 [0.80, 0.90]	1.00 [1.00, 1.00]	0.222
SE in OFF	98	0.60 [0.40, 0.70]	0.60 [0.40, 0.70]	0.60 [0.40, 0.72]	0.80 [0.75, 0.85]	0.50 [0.25, 0.70]	0.80 [0.80, 0.80]	0.177
MMSE	109	28.00 [25.00, 29.00]	28.00 [25.00, 29.00]	29.00 [26.00, 29.00]	23.00 [19.50, 26.50]	28.00 [25.00, 29.00]	29.00 [29.00, 29.00]	0.813
FAB	109	17.00 [15.00, 18.00]	17.00 [13.00, 17.00]	17.00 [15.00, 18.00]	16.50 [15.75, 17.25]	17.00 [15.00, 18.00]	18.00 [18.00, 18.00]	0.364
PDQ-39	104	43.59 [33.97, 51.28]	47.44 [40.06, 53.85]	41.03 [33.97, 48.72]	29.50 [23.10, 35.91]	42.95 [35.90, 46.15]	32.69 [32.69, 32.69]	0.139
ASBPD part II	109	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.50 [0.25, 0.75]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.852
ASBPD	109	7.00 [4.00, 10.00]	7.00 [4.00, 11.00]	7.00 [4.00, 10.00]	8.50 [7.75, 9.25]	7.00 [4.00, 12.00]	3.00 [3.00, 3.00]	0.733

Supplementary Table 3: Characteristics of patients assigned to the classes of total LEDD trajectories

var	N	all	Class 1 (a)	Class 2 (b)	Class 3 (c)	Class 4 (d)	Class (e)	p
Count		120	20 (16.67%)	5 (4.17%)	28 (23.33%)	29 (24.17%)	30 (25%)	
Gender (F)	120	60 (50.00%)	12 (60.00%)	2 (40.00%)	12 (42.86%)	15 (51.72%)	15 (50.00%)	0.806
Age at Baseline	120	64.00 [56.75, 69.00]	61.50 [54.75, 66.25]	61.00 [61.00, 64.00]	63.00 [55.25, 69.25]	68.00 [59.00, 72.00]	65.50 [55.50, 68.00]	0.506
PD Duration	120	11.00 [8.00, 15.00]	11.50 [7.75, 15.25]	13.00 [12.00, 15.00]	11.00 [8.00, 14.00]	10.00 [7.00, 14.00]	10.50 [8.25, 15.00]	0.808
UPDRS part I	109	2.00 [2.00, 4.00]	2.00 [1.00, 4.25]	2.00 [0.00, 3.00]	3.00 [2.00, 4.25]	3.00 [2.00, 4.00]	2.00 [2.00, 4.50]	0.587
UPDRS part II in ON	107	7.00 [3.00, 12.00]	9.00 [4.50, 14.00]	4.00 [3.00, 9.00]	5.00 [1.50, 12.00]	8.00 [4.00, 12.00]	7.00 [2.00, 10.50]	0.570
UPDRS part II in OFF	106	22.00 [15.00, 26.00]	19.50 [12.75, 29.25]	21.00 [18.00, 22.00]	22.00 [19.00, 27.00]	22.00 [16.00, 26.00]	21.00 [14.00, 25.00]	0.705
UPDRS part III in ON	107	17.00 [10.50, 25.00]	17.50 [12.00, 27.50]	13.00 [9.00, 17.00]	15.00 [10.50, 21.00]	17.00 [9.00, 28.00]	17.00 [12.25, 23.75]	0.688
UPDRS part IV	108	8.00 [6.00, 10.00]	10.00 [7.75, 11.00]	8.00 [7.00, 9.00]	7.50 [5.75, 9.00]	8.00 [5.75, 9.00]	9.00 [6.00, 10.50]	0.207
HY in ON	101	2.00 [1.50, 2.50]	2.00 [1.25, 2.75]	2.00 [2.00, 2.00]	2.00 [1.50, 2.50]	2.00 [1.38, 3.00]	2.00 [1.75, 2.50]	0.979
HY in OFF	98	3.00 [2.50, 4.00]	3.00 [2.50, 3.75]	3.00 [2.50, 3.00]	3.00 [3.00, 4.00]	3.00 [2.50, 4.00]	3.00 [2.12, 4.00]	0.483
SE in ON	103	0.80 [0.70, 0.90]	0.80 [0.70, 0.90]	0.95 [0.90, 1.00]	0.85 [0.80, 0.90]	0.90 [0.80, 0.90]	0.80 [0.70, 0.90]	0.253
SE in OFF	98	0.60 [0.40, 0.70]	0.60 [0.40, 0.80]	0.60 [0.40, 0.70]	0.50 [0.30, 0.67]	0.60 [0.40, 0.70]	0.60 [0.43, 0.69]	0.734
MMSE	109	28.00 [25.00, 29.00]	27.00 [24.75, 29.25]	28.00 [27.00, 29.00]	28.00 [25.00, 29.00]	29.00 [27.00, 30.00]	28.00 [24.00, 29.00]	0.559
FAB	109	17.00 [15.00, 18.00]	16.50 [12.75, 17.00]	16.00 [16.00, 18.00]	17.00 [15.00, 17.25]	17.00 [15.00, 18.00]	16.00 [14.50, 18.00]	0.862
PDQ-39	104	43.59 [33.97, 51.28]	43.27 [35.42, 57.69]	37.82 [36.54, 43.59]	44.23 [37.18, 53.53]	44.87 [32.37, 48.08]	41.99 [34.29, 49.84]	0.716
ASBPD part II	109	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.668
ASBPD	109	7.00 [4.00, 10.00]	6.50 [3.50, 10.00]	9.00 [7.00, 12.00]	7.00 [4.00, 11.25]	6.00 [4.00, 9.00]	7.00 [4.50, 10.00]	0.743

Supplementary Table 4: Characteristics of patients assigned to the classes of the trajectories of Mean Dose per Intake

var	N	all	Class 1 (a)	Class 2 (b)	Class 3 (c)	Class 4 (d)	Class (e)	p
Count		120	37 (30.83%)	49 (40.83%)	7 (5.83%)	15 (12.5%)	4 (3.33%)	
Gender (F)	120	60 (50.00%)	20 (54.05%)	23 (46.94%)	2 (28.57%)	9 (60.00%)	2 (50.00%)	0.682
Age at Baseline	120	64.00 [56.75, 69.00]	64.00 [56.00, 71.00]	66.00 [59.00, 72.00]	60.00 [57.50, 65.00]	59.00 [52.50, 63.50]	56.00 [46.75, 65.00]	0.082
PD Duration	120	11.00 [8.00, 15.00]	10.00 [8.00, 15.00]	11.00 [8.00, 15.00]	12.00 [12.00, 13.50]	11.00 [5.00, 15.50]	9.00 [8.25, 11.50]	0.861
UPDRS part I	109	2.00 [2.00, 4.00]	2.00 [2.00, 4.50]	2.00 [2.00, 4.00]	3.00 [2.50, 4.50]	2.00 [1.00, 4.00]	0.50 [0.00, 1.50]	0.245
UPDRS part II in ON	107	7.00 [3.00, 12.00]	7.00 [1.50, 11.75]	8.00 [4.00, 12.50]	3.50 [2.00, 8.00]	8.00 [4.00, 11.00]	7.50 [1.50, 13.75]	0.756
UPDRS part II in OFF	106	22.00 [15.00, 26.00]	21.50 [14.75, 28.75]	22.00 [16.50, 25.50]	24.50 [15.00, 34.75]	21.00 [12.50, 24.50]	20.00 [17.25, 21.50]	0.726
UPDRS part III in ON	107	17.00 [10.50, 25.00]	17.00 [7.50, 25.50]	16.00 [12.00, 23.50]	21.00 [14.50, 24.50]	16.00 [11.00, 24.00]	16.00 [12.00, 19.25]	0.879
UPDRS part IV	108	8.00 [6.00, 10.00]	8.00 [5.00, 9.00] d	8.00 [6.00, 10.00]	8.00 [7.50, 8.50]	10.00 [8.50, 12.00] a	7.50 [7.00, 10.00]	0.041*
HY in ON	101	2.00 [1.50, 2.50]	2.00 [1.75, 3.00]	2.00 [1.62, 2.50]	2.00 [1.25, 2.00]	2.00 [1.12, 2.00]	2.00 [1.75, 2.75]	0.658
HY in OFF	98	3.00 [2.50, 4.00]	3.00 [2.50, 4.00]	3.00 [2.50, 4.00]	4.50 [3.25, 5.00]	3.00 [2.00, 3.00]	3.50 [2.50, 4.25]	0.370
SE in ON	103	0.80 [0.70, 0.90]	0.85 [0.70, 0.92]	0.80 [0.80, 0.90]	0.92 [0.90, 0.99]	0.80 [0.80, 0.90]	0.85 [0.78, 0.92]	0.634
SE in OFF	98	0.60 [0.40, 0.70]	0.50 [0.40, 0.70]	0.60 [0.40, 0.70]	0.40 [0.20, 0.67]	0.60 [0.50, 0.70]	0.40 [0.20, 0.70]	0.748
MMSE	109	28.00 [25.00, 29.00]	28.00 [25.00, 29.00]	28.00 [25.00, 29.50]	28.00 [25.00, 28.50]	29.00 [28.00, 29.00]	27.00 [24.75, 29.25]	0.610
FAB	109	17.00 [15.00, 18.00]	16.50 [14.00, 18.00]	17.00 [13.50, 17.00]	16.00 [15.50, 17.50]	18.00 [17.00, 18.00]	16.50 [15.75, 17.25]	0.123
PDQ-39	104	43.59 [33.97, 51.28]	41.67 [36.22, 47.09]	44.87 [34.46, 51.28]	37.18 [31.09, 47.76]	48.08 [35.90, 54.49]	43.59 [34.62, 50.16]	0.663
ASBPD part II	109	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.50]	0.00 [0.00, 1.00]	0.00 [0.00, 0.25]	0.755
ASBPD	109	7.00 [4.00, 10.00]	5.00 [3.50, 7.50]	7.00 [4.75, 11.00]	8.00 [6.00, 11.00]	10.00 [4.50, 12.50]	7.50 [6.25, 9.75]	0.051

III. Qualitative study – questionnaires

Patients interviewed during the study (Virbel-Fleischman, Rétory, et al. 2020) received the French validated versions of both SUS and AttrakDiff questionnaires. The English version is presented here for consistency.

System Usability Scale (SUS)

Assess these items according to your agreement	Strongly Disagree				Strongly Agree
1. I think that I would like to use this system frequently	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. I found the system unnecessarily complex	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. I thought the system was easy to use	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. I think that I would need the support of a technical person to be able to use this system	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. I found the various functions in the system were well integrated	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. I thought there was too much inconsistency in this system	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. I imagine that most people would learn to use this system very quickly	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. I found the system very awkward to use	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. I felt very confident using the system	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. I needed to learn a lot of things before I could get going with this system	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

AttrakDiff questionnaire

Instructions: “This questionnaire is in the form of pairs of contrary words. The contrast between each word of the pairs can be subdivided in further rating levels that should be assessed spontaneously. In order to best answer this questionnaire, keep in mind that there is no right or wrong answer and try to answer as spontaneously as possible. If a term seems inappropriate to describe the system, be sure to provide an answer anyway.”

Human	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Technical
Isolating	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Connective
Pleasant	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Unpleasant
Inventive	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Conventional
Simple	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Complicated
Professional	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Unprofessional
Ugly	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Attractive
Practical	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Impractical
Likeable	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Disagreeable
Cumbersome	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Straightforward
Stylish	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Tacky
Predictable	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Unpredictable
Cheap	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Premium
Alienating	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Integrating
Brings me closer to people	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Separates me from people

Unpresentable	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Presentable
Rejecting	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Inviting
Unimaginative	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Creative
Good	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Bad
Confusing	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Clearly structured
Repelling	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Appealing
Bold	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Cautious
Innovative	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Conservative
Dull	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Captivating
Undemanding	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Challenging
Motivating	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Discouraging
Novel	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Ordinary
Unruly	<input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/> <input type="radio"/>	Manageable

IV. Qualitative study – interview guides

Interview guides for patients' first and second interviews

PATIENTS' INTERVIEW GUIDE

Context

Body-worn sensors (BWS) are devices that are placed on the body and measure body movements to deduce the type of activity performed during actions of daily life and over an extended period. In the context of Parkinson's disease, their aim is to assess the motor symptoms and to give an objective assessment of the patient's condition at home to the doctor. He can adapt the drug treatment according to the measurements made on activities and tasks of everyday life.

Study's objectives

The main objectives of this interview are:

- to know and understand the perception of patients facing BWS (the objectives of their use, their functioning)
- to understand how patients perceive and feel the use of BWS (before taking them in hand)
- to understand what patients expect from BWS and what they fear in their use

The patient profiles who will be interviewed as part of this study are patients with or without motor symptoms.

Short and quick introduction to the study (if question from the patient // not more info)

We will talk about sensors that are placed on the body and measure body movements to deduce the type of activity performed during actions of daily life and over an extended period. In the context of Parkinson's disease, they aim to assess your motor symptoms and to give an objective assessment of your condition at home. Sensors offer doctors the possibility of obtaining a report of symptoms that appear throughout the day and throughout the wearing period. This report gives an overall summary or even minute by minute of the tremors, slowdowns or even difficulties in walking that you may have suffered. They continuously and objectively measure the onset and severity of Parkinson's symptoms in real life conditions.

First interview

Introduction (10 minutes maximum)

First of all, I would like to thank you for agreeing to participate in our study and for the time you have given us.

My name is xxx and I work on the care of patients with Parkinson's disease.

We already talked about this project a while ago and you agreed to participate in this study.

As you already know, the study in which you are participating will take place in three stages:

- a first interview which takes place today
- your experience of using a BWS at home for a week
- a second interview which will take place in a week

Today, I am going to ask you some questions about your life with PD and what you think about BWS. I will show you the sensor that was selected for you, present it to you and answer your questions about the device you will bring home for one week. Then I will ask you a few questions about your feelings regarding the device. At the end of our meeting, I will explain more specifically how the sensor works so that you can use it at home. I will have you sign a consent to participate at the end of our meeting.

Have you ever heard of body-worn sensors/monitoring?

If yes: great, what is your definition?

If not: can you guess?

We have about 1h30 to talk together. We will tackle different subjects:

- first I'll ask you a few questions about yourself and your lifestyle with Parkinson's disease today (introduction)
- I will then ask you questions about what you expect from this type of device and if you have ideas of use with this technology (theme # 1)
- then I will present to you in more detail the functioning of the sensor that you will take at home
- and finally, I will ask you what you think of this technology and the objectives of the monitoring with sensors for the follow-up of Parkinson's disease (themes # 2 and # 3)

I emphasize that there is no right or wrong answer. This is not an assessment, I am interested in your personal opinion so you can be completely frank with me. I do not work for any of the manufacturers of these tools and am seeking your input. Also, you may have the impression that I insist and that I ask the same question several

times but it is precisely to identify your opinion and identify elements of your speech whether they are positive or negative.

Finally, I will need to record our conversation so that I can correctly transcribe what you are saying today so that I can talk more freely with you without taking any notes now. I confirm that this recording will only be used in the context of this study and all the information that I will collect will remain anonymous. If you want something not to be recorded, please let me know. Likewise, if there are any questions that bother you or you don't want to answer certain questions, please let me know.

Do you have any questions before we start?

Questions

General introduction (10 minutes)

Can you tell me more about yourself, introduce yourself?

What is / was your job?

What are your activities?

Can you describe one of your typical days?

Do you have a daily habit? Something you do every day?

Can you briefly describe the history of your illness?

How long have you known the diagnosis?

Can you explain what you've searched or done to better understand the disease?

Do you have difficulty describing or perceiving your symptoms?

Did you have any specific symptoms and which ones before diagnosis?

What are your main symptoms of Parkinson's disease?

Have you changed treatment often?

Would you say that you are satisfied with your treatment?

Can you give me your opinion on your medical follow-up of the disease?

How are you managed for Parkinson's disease? What do you do in particular for your Parkinson's disease?

Would you be interested in learning more about your symptoms?

What would you like to change to improve your life with the disease?

Theme #1: Understanding and expectations (5 minutes)

What do you think of using new technologies to track your disease?

Do you use technological tools for your Parkinson's disease? Which?

How would you describe your interest in new technologies?

What is the place of this type of tool in your everyday life?

Is this the first time that you are presented with sensors?

What was your first reaction to the presentation of sensors?

What is the first word that comes to mind to speak or describe these devices? Would you say it is positive or negative? Why?

Device presentation (3 minutes)

Theme #2: Perception of the follow-up by monitoring with sensors (10 minutes)

What does this device inspire you? How do you react to this sensor?

What impressed you most about my presentation on BWS monitoring? What do you remember?

To what extent do you think this will be useful to you?

Can you give me examples of situations that you think could benefit from monitoring with sensors?

Can you give me examples of cases where monitoring with sensors might not be a good tool for monitoring Parkinson's disease?

How do you think wearing a sensor on your body to record your symptoms will be an advantage/disadvantage?

Do you think of features you would like to see with disease monitoring tools?

How do you live with getting a tool to track your illness for a week? And having to wear the device on your body every day after our interview?

Do you have anything to add?

Theme #3: Expectations and perspectives (10 minutes)

What are your expectations for this week of recording with such a device?

What is your opinion on monitoring the disease using technologies such as sensors?

Would you say that you are interested in the results of the monitoring? Would you be interested in understanding the reports obtained? Why?

What impact do you feel from sensor monitoring on managing motor symptoms?

What value do you see in sensor monitoring?

Do you think that the use of sensors could concern you outside of this study?

Do you think that following the evolution of your disease with these types of devices can improve your living conditions with the disease?

What do you think you would use it for if you had this device?

What are your expectations for BWS monitoring in general?

Do you have any other ideas to add? Any other comments?

Outro (5 minutes)

Manipulation of the device (5 minutes)

Second interview

Introduction (10 minutes)

First of all, I would like to thank you for agreeing to participate in our study and for the time you have given us.

We have about 1 hour before us to chat together. We will tackle different subjects:

- first I will ask you a few questions about yourself and your lifestyle with Parkinson's today (introduction)
- I will then ask you questions about what you learned from your handling of the device (themes # 1 and # 2)
- I will then ask you for your idea on the objectives of BWS monitoring for the follow-up of Parkinson's disease (theme # 3)

I emphasize that there is no right or wrong answer. This is not an assessment, I am interested in your personal opinion so you can be completely frank with me. I do not work for any of the manufacturers of these tools and am seeking your input. Also, you may have the impression that I insist and that I ask the same question several times but it is precisely to identify your opinion and identify elements of your speech whether they are positive or negative. I want to warn you that you may have the impression that I am forcing you to say something but be confident, I will only force you to tell me what you have experienced or felt and to express your feelings and describe your experience in detail.

Finally, I will need to record our conversation so that I can correctly transcribe what you are saying today so that I can talk more freely with you without taking any notes now. I confirm that this recording will only be used in the context of this study and all the information that I will collect will remain anonymous. If you want something not to be recorded, please let me know. Likewise, if there are any questions that bother you or you don't want to answer certain questions, please let me know.

Do you have any questions before we start?

Questions

General introduction (3 minutes)

Have you changed your habits about the disease since the last time?

How did the week go about your symptoms, fatigue, etc.?

Do you have anything else you would like to share with me regarding our first interview about your illness?

Theme #1: Feedback on the use of a sensor for one week (10 minutes)

How would you describe your week with the device?

What is the first word that comes to mind to describe this week?

Was your first experience with the device positive or negative? Can you explain why?

How did you experience handling the sensor for a week? Can you describe the handling that you had of it?

What encouraged you to continue using the device?

What made you stop using the device?

What is your point of view on the design / ergonomics of the device?

How did you experience the handling and installation / removal of the device every day?

Did the device bother you or was it uncomfortable at specific times / all the time? Can you give me concrete examples?

Did you experience wearing / handling the device as a constraint? Was wearing the device all day complicated?

What were these constraints linked to the device in everyday life? At particular times?

For example, were you embarrassed when washing, having to take it off and putting it back on, or when dressing or putting on a coat?

Theme #2: Perception of the follow-up with sensors (5 minutes)

Have you talked about the monitoring with sensors around you? To your loved ones?

If yes, how did you present the device? What were the comments? And how did you take these remarks?

If not, have you received comments without your mentioning them? Have some people noticed that you are wearing a device? Did you mind that the device was visible?

Have you noticed any changes in your behavior due to the wearing of the device, in the performance of your daily activities?

What do you think about the fact that the movements that you performed at a given time are monitored over several days?

Do you think of anything else you would like to share about this device experience?

Theme #3: Expectations and perspectives (5 minutes)

What are your expectations from monitoring now that you've used the device?

What is your opinion on monitoring the disease using technologies such as sensors?

What impact do you feel from the monitoring on managing motor symptoms?

What value do you see in monitoring with sensors now?

If I let the device to you now, do you think you will use it?

Do you think that the monitoring with sensors could concern you outside of this study?

Do you think that following the evolution of your disease with these types of devices can improve your living conditions with the disease?

If you had this device, what use do you think you would have of it?

In one word, what is your perception of the monitoring with sensors in general?

Do you think of features of the system that you want to improve or change?

Do you think of features you would like to add to this tool now that you know it better?

Give examples if negative answer: read the time on the watch, give an indication when the walking is bad, etc...

And ask: Why did you not think about it? / What is the reason why you like this idea?

If not this device, what do you think would be the ideal tool to measure the motor symptoms of Parkinson's disease?

Do you have any other ideas to add? Any other comments?

Test the usability and attractiveness of the technology

Two questionnaires filling: SUS and ATTKDIFF

Outro (5 minutes)

Interview guides for health professionals' interview

HEALTH PROFESSIONALS' INTERVIEW GUIDE

Context

Body-worn sensors (BWS) are devices that are placed on the body and measure body movements to deduce the type of activity performed during actions of daily life and over an extended period. In the context of Parkinson's disease, their aim is to assess the motor symptoms and to give an objective assessment of the patient's condition at home to the doctor. He can adapt the drug treatment according to the measurements made on activities and tasks of everyday life.

Study's objectives

The main objectives of this study are:

- to know and understand the perception of neurologists and nurses facing monitoring devices (the objectives of their use, their functioning)
- to understand how healthcare professionals perceive and feel the use of monitoring (before using them)
- to understand the expectations and fears related to the system

Introduction (10 minutes)

First of all, I would like to thank you for agreeing to participate in our study and for the time you have given us.

My name is xxx and I work on the care of patients with Parkinson's disease.

We will tackle different subjects during our discussion:

- I am going to ask you a few questions about yourself and how you work for monitoring Parkinson's patients today (introduction)
- I will then ask you questions about what you know about BWS monitoring and what is your perception (themes # 1 and # 2)
- and finally, I will ask you about your expectations of this technology (theme # 3)

I emphasize that there is no right or wrong answer. This is not an assessment, I am interested in your personal opinion so you can be completely frank with me.

Finally, I will need to record our conversation so that I can correctly transcribe what you are saying today so that I can talk more freely with you without taking any notes now. I confirm that this recording will only be used for the purposes of this study and all the information that I will collect will remain anonymous. If you want something

not to be recorded, please let me know. Likewise, if there are any questions that bother you or you don't want to answer certain questions, please let me know.

Do you have any questions before we start?

Questions

General introduction (5 minutes)

Would you say that you are satisfied with the technical means you have for patients' follow up in their Parkinson's disease?

Can you give me your opinion on methods for monitoring the disease?

What would you like to change to improve your patient follow-up?

How would you describe your practice of new technologies? What is the place of this type of tool in your clinical practice?

Theme #1: Understanding and expectations (5 minutes)

What do you think of the use of new technologies to monitor chronic conditions?

Have you ever heard of BWS monitoring?

If yes: what is your definition?

If not: can you guess?

Is this the first time you've been involved in a project with BWS?

If yes, what is your reaction?

If not, what was your first impression?

Have you changed your perception of BWS monitoring? What is it today?

Presentation of the three devices and respective reports (3 minutes)

Theme #2: Perception of the follow up by monitoring with sensors (8 minutes)

What is your opinion on monitoring Parkinson's disease using technologies such as BWS?

How useful do you think BWS monitoring currently is for you?

Can you give me some examples of situations that you think could benefit from BWS monitoring?

Can you give me examples of cases where BWS monitoring might not be a good tool for Parkinson's disease follow up?

How do you think getting the patient to wear a BWS to record their symptoms will be:

an advantage for your practice and/or for the patient?

a disadvantage for your practice and/or for the patient?

Do you think of features you would like to see with disease monitoring tools?

Do you have anything to add?

Theme #3: Expectations and perspectives (7 minutes)

What are your expectations for BWS monitoring in general?

What value do you see in BWS monitoring?

Do you see a use rather oriented towards current practice? Can you give me concrete cases?

Or research? Do you have any examples to give me?

What impact do you feel from BWS monitoring on managing motor symptoms?

Do you think that the use of BWS could concern you?

Do you think that following the progress of your patients with this type of device will improve your working conditions? If yes, how? If not why?

What do you think you would use it for if you had this device for your practice?

Do you have any other ideas to add? Any other comments?

Outro (5 minutes)

V. Detailed methodology applied to the study « Motor symptoms assessment and treatment adaptation in Parkinson's disease based on body-worn sensor report: what is the agreement among neurologists? »

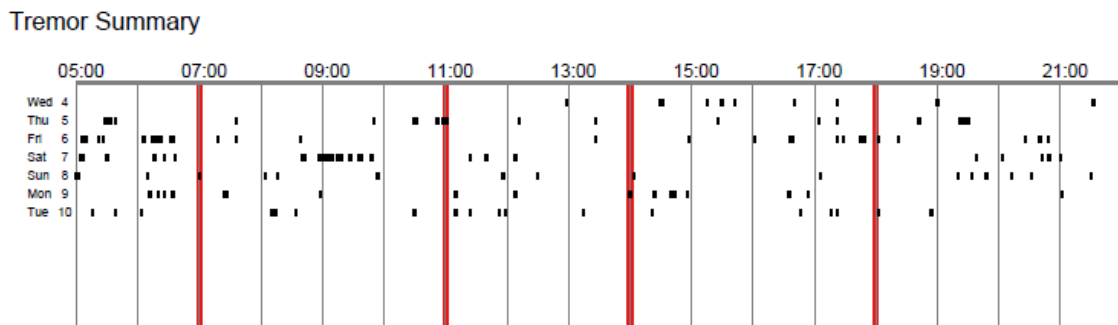
In this section, we provide additional information regarding methodology used in (Virbel-Fleischman, Mousin, et al. 2020). Especially, three elements are further described.

First, regarding the questionnaire answers a few clarifications may facilitate the understanding. Interpretation of the PKG® was executed on the basis of 30-minute periods for consistency with the format of patient diaries in real-life settings. Thus, detections of symptoms indicated by raters were distinguished for each period of 30 minutes. Then, if an exact time was expressed for a symptom occurrence (*e.g.* 8.00 or 11.30), it was extended to the next 30-minute interval for homogeneity of analysis (*e.g.* 8.00 - 8.30 or 11.30 - 12.00). Moreover, regarding the suggestions for treatment adaptation, raters indicated their decision (total oral dose required, number of intakes, duration of the pump delivery and apomorphine flow rate(s)) and type of change (stable / increase / decrease / establishment / stop / not applicable) for each suggested modification. They also signaled if the detected symptom was perceived crucial for each patient's case, and if it was used while suggesting treatment modification.

Then, two types of continuous scores were obtained from PKG®. Continuous scores related to bradykinesia and dyskinesia were computed from the reading of PKG® main graph curves. Similarly, severity scores for bradykinesia and dyskinesia were defined for each period of 30 minutes along the monitoring period. A severity level for each 30-minute period from 5 A.M. to 10 P.M. was determined thanks to the prevalence of the curve in the zone. In the case of equivalence of two severity levels within the 30-minute period, adjacent evolution of the curve was considered (importance of increase or decrease, in the previous or next period). Same

technique was used for the median curve and the third quartile of both bradykinesia and dyskinesia displays.

Finally, a continuous tremor score was created to complete PTT. The Tremor Score represented the percentage of tremor per hour and was obtained thanks to an image analysis of the PKG® tremor graph (Supplementary Figure 1). The color matrix of the graph was analyzed and three main intensities were described (grey, black and red). By subtraction, we selected each type of element in the graph: global frame and legends in grey, medication intakes in red, and tremor occurrence in black. We extracted the global frame (removing legends) and scanned each pixel to detect the dots representing tremor. For each individual hour, we detected the black dots sizes, which were reported to the number of monitoring days (*i.e.*, 7 days for all patient cases). Thus, the percentage occupied by black dots for each hour was computed, resulting in the percent of time with tremor per hour. This analysis was performed with Matlab ® version R2019b.



Supplementary Figure 1: Example of the PKG® tremor graph

VI. Patient cases PKG® information for the analysis of the PKG® reading

Patients	n°1	n°2	n°3	n°4	n°5	n°6	n°7	n°8
Mean BKmed	2.3	1.9	1.4	2.8	1.1	1.9	2.6	2.0
Mean BK75	3.3	2.5	2.3	3.6	2.0	1.9	3.5	2.6
Mean DKmed	1.6	2.2	1.6	1.0	2.5	1.8	1.2	1.9
Mean DK75	2.4	3.0	2.4	1.3	3.4	2.5	2.1	2.5
BK 1	40	47	56	22	65	38	23	46
BK 2	16	34	26	27	17	30	24	29
BK 3	24	12	13	28	9	21	26	16
BK 4	20	7	6	23	9	11	27	8
DK 1	40	22	44	74	27	32	55	37
DK 2	21	23	29	18	22	29	24	28
DK 3	14	32	18	5	22	23	18	23
DK 4	24	23	9	3	28	15	3	12

Supplementary Table 5: Patient cases PKG scores

VII. Questionnaire to the raters

For the evaluation of PKG® reading and decisions on treatment action, a two-part questionnaire was filled in by raters. The first part was related to PKG® reading and the second part was dedicated to the suggestions of treatment adaptation. An example of the questionnaire for the patient's case n°5 was translated in English for consistency.

Reading grid for treatment adaptation of Patient Case n°5

PKG Analysis

Reminder:

- *BK: bradykinesia*
- *BKS: bradykinesia score (I, II, III or IV)*
- *DK: dyskinesias*
- *DKS: dyskinesias score (I, II, III or IV)*
- *FDS: fluctuation dyskinesia score*
- *PTI: percent of time immobile*
- *PTT: percent of time with tremor*

Identify the target symptoms measured by the PKG Watch, their occurrences and periods of onset during the day.

Indicate what elements justify your decisions to modify treatment or the lack of therapeutic action.

Symptoms	Target	Number of occurrence per day	Manifestation periods	Justifies adaptation
Fluctuations	<input type="checkbox"/> Yes <input type="checkbox"/> No			<input type="checkbox"/> Yes <input type="checkbox"/> No
Dyskinesias	<input type="checkbox"/> Yes <input type="checkbox"/> No			<input type="checkbox"/> Yes <input type="checkbox"/> No
Tremor	<input type="checkbox"/> Yes <input type="checkbox"/> No			<input type="checkbox"/> Yes <input type="checkbox"/> No

Comments on the PKG

.....

.....

.....

.....

Information to be transmitted to the patient (for example, punctuality reminder of the intake, comments on the adjustment, a next visit, etc.)

.....

.....

.....

Indicate below the suggested therapeutic modifications that you wish to carry out concerning the anti-parkinsonian treatment from this patient file. A single therapeutic decision is required, knowing that it can combine several therapeutic actions within the limits of usual practices. A therapeutic decision may also be to leave the treatment in progress without modification.

Conventional treatment modification(s)

Treatment class	On going	Treatment name	Total dose adjustment	Total dose suggested	Number of intakes adjustment	Number of intakes suggested
L-Dopa	<input checked="" type="checkbox"/>		Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
Dopaminergic agonists	<input checked="" type="checkbox"/>		Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
Anticholinergics			Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
Amantadine	<input checked="" type="checkbox"/>		Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
IMAO-B	<input checked="" type="checkbox"/>		Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
ICOMT			Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	

Apomorphine pen			Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
Clozapine			Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
Antidepressants			Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	
Other(s)	<input checked="" type="checkbox"/>		Stable Increase Decrease Instauration Not applicable		Stable Increase Decrease Instauration Not applicable	

Continuous Subcutaneous Apomorphine Infusion modification(s)

Before adjustment		After adjustment	
Duration of treatment per day	<input checked="" type="checkbox"/> Continuous between 7am and 11pm	Duration of treatment per day	<input type="checkbox"/> Continuous between and
	<input type="checkbox"/> Continuous 24/24		<input type="checkbox"/> Continuous 24/24
Infusion rate(s)	Flowrate 1 5 mg/h Flowrate 2 6 mg/h Flowrate 3 mg/h	Infusion rate(s)	Flowrate 1 mg/h Flowrate 2 mg/h Flowrate 3 mg/h

VIII. Accelerometer-based measures and analyses of gait and respiratory parameters: towards a new assessment for Parkinson's disease patients

INTRODUCTION

While motor dysfunctions are the cardinal symptoms of Parkinson's disease (PD), patients suffer from various non motor symptoms (NMS). They represent a heavy burden in PD patients and are often under-recognized and properly considered for treatment adaptation. Among NMS, dysautonomic manifestations like cardiac frequency or blood pressure are monitored by continuous objective measures. Respiratory signs are less commonly reported but can occur. PD patients might report pulmonary discomfort in the late stages of the disease while PD can cause a range of dysfunctions linked to breathing even early in PD course (Baille et al. 2018). Discussions agree listing various respiratory disorders in PD that may be classified as upper airway obstruction, restrictive disorders, complications of medications intake, complications of medication withdrawal, and aspiration pneumonia, which is considered as the most frequent cause of death among PD patients (Hoehn and Yahr 1967; Sabaté et al. 1996; Nóbrega, Rodrigues, and Melo 2008a; 2008b). Breathing is at the interface between motor and vegetative systems, and PD affects both (Brown 1994; Garcia-Borreguero, Larrosa, and Bravo 2003). Bradykinesia and rigidity are frequently incriminated for respiratory complaints as they may decrease chest compliance (Monteiro et al. 2012). The impact of dopaminergic treatments on respiratory parameters is debatable (Monteiro et al. 2012; Pal et al. 2007; De Bruin et al. 1993) and the characterization of breathing function differences between ON- and OFF-drug requires more investigations (Hampson et al. 2017). Studying respiratory parameters in PD may then inform about motor states and autonomic nervous system dysfunctions, and an accurate estimation of respiratory parameters is essential for obtaining quantitative information on non-motor deficits in PD, which could help determine disease progressions and therapeutic decisions.

Spirometry remains the first chosen method to study respiratory functions during daytime but has some limits. It is mostly performed in a static position and relies on the maximum lung capacity as the patient is forced to exhale, which can be difficult for elderly subjects and may not show correct reproducibility in PD patients (De Bruin et al. 1993). Spirometry might not report long term and continuous monitoring of real-life conditions.

On the other hand, polygraphy is widely used to diagnose respiratory sleep disorders. For example, even though the relation between PD and Obstructive Sleep Apnea (OSA) remains controversial (Trotti and Bliwise 2010; Crosta 2017), studies with polygraphy technique have documented apnea or hypopnea in PD patients and this technique has been used for studies of respiratory parameters measured during activities in specific diseased populations (Rétory, Niedziałkowski, et al. 2016; Rétory, de Picciotto, et al. 2016; Rétory et al. 2017). Information regarding activity, respiratory inductive plethysmography measures, nasal pressure, cardiac frequency and pulse oximetry can be obtained. Thus, polygraphs might then allow tackling the issues of measurement techniques for respiratory function since they can record breathing parameters continuously during free movements. Moreover, using a non-invasive and non-demanding tool for respiratory studies may be a solution for continuous measures of respiratory parameters in PD patients. The combination of PD motor symptoms assessment and respiratory disorders evaluation with a polygraph might be of interest.

This study aimed at analyzing the feasibility of characterizing simultaneous respiratory and locomotor parameters in healthy subjects using a smart wearable polysomnography system as a prerequisite for a study in PD patients.

METHODS

We combined a polygraph (Nox A1 Sleep Monitor, Nox Medical, Reykjavik, Iceland) composed of a set of two sensors attached to the thorax and chest with straps and nasal cannulas, with an oximeter to study breathing behaviors at rest and during walk (Figure 1).

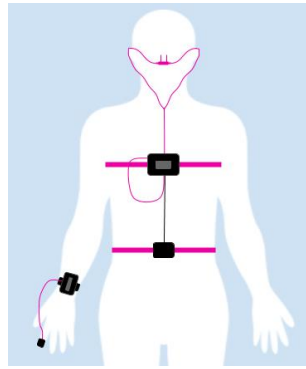


Figure 1: Polygraphy system installed on the healthy subject

We monitored 6 healthy subjects for 15 minutes and in four conditions with the polygraph and the oximeter. Subjects were asked to remain seated for 5 minutes, to walk freely and at a free pace during 2.5 minutes (free walk), to go back and forth along a straight pathway for 2.5 minutes (walk test), and finally to perform free activities during the last 5 minutes (free activities). Analysed parameters are indicators of locomotion (cadence, number of steps, step length, etc) and of breathing (respiratory rate, relative mean inspiratory flow, relative ventilation, duty cycle, etc). The results were analyzed with the dedicated software (Noxturnal) and Matlab ® version R2018b.

RESULTS

The results are indications of the tendency of parameters across conditions and across subjects. Results are presented as mean \pm standard deviation. Respiratory parameters are presented in Table 1. They are relative data, we used the seated position as reference.

	Respiratory Rate	Relative Tidal Volume	Duty Cycle	Mean Inspiratory Flow
Seated	21.91 \pm 3.61	21.36 \pm 8.48	0.41 \pm 0.06	1.03 \pm 0.05
Free Walk	25.07 \pm 5.38	27.00 \pm 11.08	0.42 \pm 0.03	1.43 \pm 0.33
Walk test	24.03 \pm 6.70	31.15 \pm 16.13	0.41 \pm 0.02	1.52 \pm 0.28
Free Activities	22.07 \pm 5.50	28.85 \pm 18.20	0.41 \pm 0.04	1.29 \pm 0.24

Table 1: Respiratory parameters of the six healthy subjects in the four conditions (mean and standard deviation).

The respiratory rate is the number of breaths per minute. The relative tidal volume is the volume of air displaced between inhalation and exhalation and reflects the flow of air that passes through the lungs. The duty cycle is the variation rate between effort (inhalation) and rest (exhalation) within the breathing cycle.

During the walk test condition, the accelerometer signals revealed for the 6 subjects:

- Cadence: 93.5 ± 7.9 steps/minute
- Step length: 54.4 ± 6.4 centimeters
- Speed between turns: 94.4 ± 12.1 cm/s

CONCLUSION

The relative tidal volume seemed to increase with activity. Undoubtedly, exercise induces an increase of ventilation, which is observed in those results. The variability of the relative tidal volume also increased and remained high during free activities, which might be explained by an insufficient period of time to return to normal reference. The mean inspiratory flow allows analysis of the respiratory drive depending on the condition. These results reveal an increase in the effort of the respiratory muscles during mild activity compared to rest. However, large variabilities in the results may reflect the small sample size. Parameters regarding movement could be measured and analyzed during specific conditions with a polygraph.

This exploratory study was an insight to the feasibility of combined assessments of motion and respiratory parameters at rest and during mild activities. Mobility phases could be interpreted independently and the respiratory parameters may be related to them thanks to this new method that we present. Thus, the association between breathing and locomotion can be studied with a polygraph, which could enable studying pattern differences between rest and mild activities in patients, and between different conditions such as ON and OFF phases. We focused on parameters that seemed to be of interest for the study of respiratory dysfunction in PD patients and of the effect of dopaminergic treatment. For instance, an insight of the recruitment of respiratory muscles in PD in various conditions would show the impact of motor states on non-motor symptoms. Also, the polygraph may be useful for sleep events detection in PD patients and it might also be efficient for the observation of the transition between ON

and OFF during sleep, and for diagnosis of respiratory dysfunction. The same study protocol might be reproduced with patients at rest and during mild activities in ON and OFF states, for a longer period of time to provide an innovative continuous and objective monitoring of breathing features in PD patients.

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