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Improvement of apathy in early Parkinson's disease

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Apathy is a disabling symptom in Parkinson's disease (PD). The effect of dopaminergic treatment on apathy is inconsistent, depending on the stage of the disease, the type of apathy and strongly influenced by placebo effect. Our study assessed the evolution of a cohort of 86 de novo, drug naive PD patients for 4 years, after dopaminergic treatment introduction. The main objective of the study was the change of apathy from baseline to follow-up and secondary outcomes were the change of other neuropsychiatric symptoms. At 4 years there was an improvement of apathy ($p = 0.002$), mainly driven by improvement of baseline apathy ($p = 0.001$). This was associated with an improvement of anxiety ($p = 0.001$), an increase in hyperdopaminergic behavior including nocturnal hyperactivity with consecutive diurnal sleepiness ($p = 0.001$ and $p < 0.001$), independently of the presence of apathy at baseline. These findings confirm, in a large real-life cohort, that dopaminergic treatment improves motivational apathy in early PD.

Neuropsychiatric symptoms represent an important burden in Parkinson's disease (PD) and are associated with decreased quality of life[1]. Apathy, anxiety and depression can occur in the premotor phase of the disease, sometimes preceding motor onset by several years[2–4]. In the early stages of the disease, this triad seems mainly related to the mesolimbic and mesocortical dopaminergic denervation, therefore defined as hypodopaminergic[5–7], and also to serotonergic system dysfunction[8]. Hypodopaminergic symptoms have been proposed to be on the one extreme of the behavioral spectrum of PD, the opposite extreme being represented by hyperdopaminergic behavior, including impulsive compulsive behaviors (ICB), dopamine dysregulation syndrome (DDS), (hypo)-mania and psychosis, which are related to the sensitization of the dopaminergic system and to dopaminergic medication[9,10].

In more advanced stages, apathy, anxiety and depression might be the result of the cortical spreading of Lewy body pathology and of a widespread cholinergic degeneration, and are associated with cognitive decline[11–14].

Apathy is a complex neuropsychiatric syndrome, presenting as a loss of motivation and interest and a reduced goal-directed behaviors[15–18]. It can occur as an isolated symptom, or as part of a larger hypodopaminergic behavioral spectrum associated with depression and/or anxiety[17,19] or, in later PD stages, with cognitive decline[13]. As a syndrome, apathy might represent the common expression of different pathophysiological processes. Several studies have suggested the implication of the dopaminergic system. Indeed, in a randomized controlled study performed in PD patients treated with subthalamic stimulation, postoperative apathy due to marked decrease of antiparkinsonian drugs was improved with dopaminergic treatment[20–22]. However, other studies provided inconsistent results on the effect of dopaminergic medication on apathy, especially at disease onset[23,24]. This could be related to methodological problems and to a strong placebo effect. One of the main issues is that many studies include non-homogenous populations with early and advanced disease, resulting in possibly, mixed motivational and cognitive apathetic syndromes[25]. Targeting de novo PD has the

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advantage of focusing mainly on motivational apathy, which has been related to dopaminergic and serotonergic deficit[8,20,26,27]. Recently, we conducted a large observational study on the evolution of neuropsychiatric symptoms in de novo, drug naïve, PD patients, the honeymoon study. Within this cohort, we performed a 6 months double-blind placebo controlled study, which failed to demonstrate the efficacy of rotigotine on apathy[24]. Here we present the 3-5 years follow-up of a subgroup of the patients initially included in the honeymoon study, and thus homogenous for disease stage, evolution, without cognitive impairment or device-aided therapies, with the objective to assess the evolution of apathy and other neuropsychiatric symptoms as a result of real-life treatment strategies.

Results

90 patients were assessed both at baseline before the introduction of dopaminergic treatment and at follow-up, 4 of whom were erroneously included since their Mattis Dementia Rating Scale (MDRS) score was <130 at follow-up. 86 patients were finally included in the analysis (34 with apathy at baseline according to the Starkstein apathy score ≥ 14). Mean follow-up duration was 4.25 years ± 0.60.

Demographic characteristics of patients, as well as MDS-UPDRS scores, cognitive scores, and dopaminergic medication are reported in Table 1.

Table 1 | Characteristics of patients

Number of pt. 86	Baseline	Follow up	*p*-value
Age	61 [55–65]	65 [60–71]	
Gender (Male/Female)	47/39	47/39	
MATTIS DEMENTIA RATING SCALE (MDRS)	141 [138-142]	141 [138-142]	0.7
FRONTAL ASSESSMENT BATTERY (FAB)	17 [16–18]	17 [16–18]	0.55
MDS-UPDRS I	8.3 (5.0)	10.7 (5.3)	<0.001
MDS-UPDRS II	7.7 (4.9)	10.0 (4.8)	<0.001
MDS-UPDRS III	27 (9.3)	31.0 (9.5)	<0.001
MDS-UPDRS IV	0	2 [0-5]	<0.001
Non-motor fluctuation ON [N. ≥ 1]	0 [0-0] [1]	0 [0–0] [10]	
Non-motor fluctuations OFF [N. ≥ 1]	0 [0-0] [4]	0 [0–1] [26]	
Total Levodopa equivalent dose		483 [350–700]	
Total dopamine agonists equivalent dose		150 [0–240]	
Rasagiline (N.)	20	49	
Benzodiazepine (N.)	10	12	
Antidepressant (N.)	11	11	
Clozapine (N.)	0	2	

Mean (standard deviation), median [interquartile range].

Apathy

There was a decrease of apathy, measured by Starkstein apathy scale, at last follow-up (12.6 ± 5.7 at baseline vs. 10.9 ± 5.6 at 4 years, $p = 0.002$, effect size = 0.30 (Confidence Interval (CI) 95%, 0.00; 0.60)). When correcting for baseline apathy, there was a significant interaction between apathy and time on the Starkstein apathy score ($p < 0.001$), with a greater reduction of apathy in the group of patients with apathy (Table 2 and Fig. 1).

Anxiety

When using the STAI, there was a significant improvement of both STAI state and trait at final visit in the whole population (STAI state 35.2 ± 9.7 at baseline, 31.1 ± 9.1 at 4 years, $p < 0.001$, effect size = 0.44 (CI 95%, 0.14; 0.74), and STAI trait 43.2 ± 10.8 at baseline, 39.1 ± 10.3 at 4 years, $p < 0.001$, effect size = 0.38 (CI 95%, 0.08; 0.68)). When considering the presence of baseline apathy, there was no significant interaction between apathy and time on the STAI score (Table 2).

Depression

There was no significant change at 4-years in depression as measured with the BDI-2 scale in the overall sample (10.2[5–16] at baseline, 9[6–15] at 4 years, $p = 0.67$, effect size = 0.04 (CI 95%, 0.00; 0.34)).

When correcting for the presence of baseline apathy, a reduction of depression was only observed in the subgroup of patients with baseline apathy ($p = 0.008$, Table 2).

Fatigue

There was no change in fatigue score with evolution of the disease (PFS-16 score 45 ± 17.2 at baseline, 47.2 ± 15.0 at 4 years, $p = 0.28$, effect size = 0.14 (CI 95%, 0.00; 0.43)). Taking into account the presence of baseline apathy, no significant interaction between time and apathy was found on the evolution of fatigue ($p = 0.07$,Table 2).

Hyperdopaminergic behaviors

There was an overall increase in hyperdopaminergic behaviors at last follow-up (Table 3, Fig. 2).

There was a significant increase from 16 patients with at least one hyperdopaminergic behavior at baseline (7 with nocturnal hyperactivity, 3 with eating disorder, 2 with hypersexuality, 1 with hypomania, 1 with creativity and 1 with hobbyism 19%, 1 with medication addiction) to 51 (59%) at last follow-up ($p = 0.001$, odds ratio= 8.0 (CI 95%, 3.2; 26.0)) (Fig. 2).

Among hyperdopaminergic behaviors, at 4-years, nocturnal hyperactivity was the most frequent (26 patients, 30%, $p = 0.001$, odds ratio= 5.8 (CI 95%, 2.0; 22.9)), followed by compulsive shopping (12%, $p = 0.01$, odds ratio= 6.0 (CI 95%, 1.3; 55.2)), hobbyism (10 patients, 12%, $p = 0.004$), eating disorder (9 patients, 10%, $p = 0.07$, odds ratio= 7.0 (CI 95%, 0.9; 315.5)), punding (7 patients, 8%, $p = 0.02$), hypersexuality (6 patients, 7%, $p = 0.29$), creativity (6 patients, 7%, $p = 0.03$), pathological gambling (5 patients, 6%, $p = 0.06$). Dopaminergic addiction was not frequent in our cohort (2 patients, 2%, $p = 0.99$).

When correcting for baseline apathy, no difference in the evolution of hyperdopaminergic behaviors was found.

Diurnal sleepiness

There was a significant increase in the diurnal sleepiness over time (ASBPD 0[0-0] (15 patients) at baseline vs. 1[0-1] (48 patients) at 4 years $p < 0.001$, effect size = 0.76 (CI 95%, 0.45; 1.07)). When considering initial apathy, no significant interaction was found between apathy and time on the evolution of diurnal sleepiness.

Neuropsychiatric fluctuations

Neuropsychiatric fluctuations became more frequent with disease evolution, with patients rather reporting OFF-dysphoria (30%) than ON euphoria (10%) (Table 1). Their frequency was slightly higher in patients with baseline apathy (35% versus 26%, Table 2).

Quality of life

At 4 years there was a significant worsening of quality of life in the whole population (PDQ39 summary index 21.7[12.9–31.2] at baseline vs. 25.3 [17.1–33.9] at 4 years, $p = 0.003$, effect size = 0.29 (CI 95%, 0.00; 0.059)). When considering initial apathy, there was no interaction between apathy and time on the change of quality of life.

Concerning different domains of the PDQ39, at last follow-up there was a significant improvement of emotional well-being (41.7[25–50] at first visit vs. 33.3[20.8–45.8] at last follow-up, $p = 0.02$, effect size = 0.26 (CI 95%, 0.00; 0.56)), and a significant worsening of: mobility (11[5–27.5] at first visit vs. 25 [10–37.5] at last follow-up, $p < 0.001$, effect size = 0.38 (CI 95%, 0.08; 0.68)), social support (0[0–16.7] at first visit vs. 8.3 [0-25] at last follow-up, $p = 0.02$, effect size = 0.27(CI 95%, 0.00; 0.57)), cognition

Table 2 | Evolution in patients with and without baseline of apathy

	Patients with baseline apathy (N = 34)		Group without baseline apathy (=52)	
	baseline	4 years	baseline	4 years
Starkstein apathy scale	18.4 (4.0)	13.7 (6.3)	8.8 (2.6)	9.0 (4.1)
STAI state	38.1 (9.9)	34.5 (10.9)	33.3 (9.2)	28.9 (7.0)
STAI trait	50.7 (8.8)	44.9 (10.7)	38.2 (9.1)	35.4 (8.2)
BDI-2	16 [11–21]	12 [9–19]	6 [3–10]	7.5 [4–12.5]
Fatigue (PFS-16)	57.3 (12.5)	55.1 (12.4)	37.0 (15.1)	42.0 (14.3)
PDQ-39 SI	30.3 [22–34.2]	32.2 [25.2–39.1]	15.4 [8.4–24.2]	21.6 [11.3–27.2]
PDQ-39 Mobility	20 [10–35]	32.5 [15–45]	7.5 [2.5–21.3]	15 [6.3–28.8]
PDQ-39 ADL	20.8[12.5–41.7]	29.2 [16.7–41.7]	12.5 [4.2–25]	16.7 [8.3–31.3]
PDQ-39 Emotional well-being	50 [37.5–62.5]	41.7 [29.2–58.3]	33.3 [16.7–47.9]	29.2 [16.7–37.5]
PDQ-39 stigma	25 [12.5–43.8]	25 [12.5–43.8]	18.8 [6.3–31.3]	25 [12.5–43.8]
PDQ-39 social support	0 [0–25]	8.3 [0–33.3]	0 [0–8.3]	0 [0–20.8]
PDQ-39 Cognition	25 [12.5–43.8]	31.3 [25-43.8]	12.5 [0–25]	18.8 [12.5–31.3]
PDQ-39 Communication	25 [8.3–41.7]	20.8 [8.3–33.3]	0 [0–12.5]	16.7 [0–33.3]
PDQ-39 Bodily disconfort	41.7 [25–58.3]	50 [33.3–66.7]	25 [12.5–37.5]	33.3 [20.8–41.7]
LEDD		550 [400–750]		443 [300–665]
DA dose		150 [0–240]		135 [0–240]
Neuropsychiatric OFF fluctuations [N. of patients]		0 [0–1] [12]		0 [0–1] [14]
Neuropsychiatric ON fluctuations [N. of patients]		0 [0–0] [5]		0 [0-0] [5]

Mean (standard deviation) for normally distributed variables, Median [interquartile range] for non-normally distributed variables. *LEDD* levodopa equivalent daily dose, *DA dose* dopamine agonist equivalent dose.

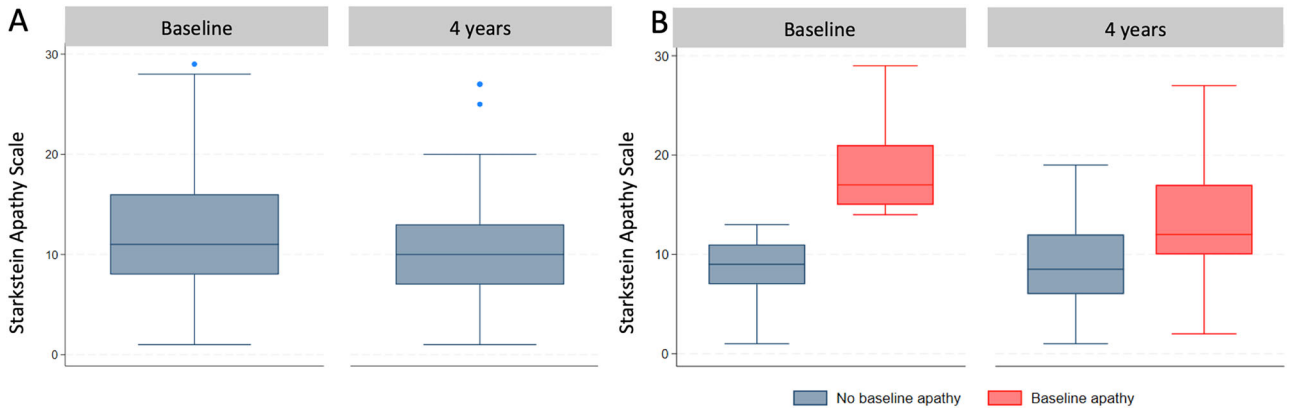

Fig. 1 | Evolution of apathy. A Change of Starkstein apathy score at 4 years. **B** Change of Starkstein apathy score by baseline apathy.

(18.8[6.3-37.5] at first visit vs. 25[18.8–37.5] at last visit, $p < 0.001$, effect size = 0.36 (CI 95%, 0.06; 0.66)) and communication (8.3[0–29.5] at first visit vs. 16.7[0–33.3] at last visit, $p < 0.001$, effect size = 0.31 (CI 95%, 0.01; 0.61)). There was a trend in worsening of stigma (18.8 [6.2–31.3] at first visit vs. 25 [12.5–43.8] at last follow-up $p = 0.05$, effect size = 0.26 (CI 95%, 0.00; 0.56)).

Looking at the impact of baseline apathy, a significant interaction between apathy and time in the stigma and communication domains was found ($p = 0.03$ and 0.003 respectively, Table 2) with a worsening only in the group without baseline apathy.

The role of dopaminergic medication dose

The post-hoc analysis with a mixed model REML did not show any significant interaction between levodopa equivalents dose or dopamine agonists equivalents dose and the evolution of apathy, and other behaviors over time.

Discussion

Our study showed an improvement of apathy in a cohort of de novo PD at 4 years of follow-up, after introduction of dopaminergic treatment. The overall improvement of apathy was mainly driven by the improvement in patients with baseline apathy, without occurrence of apathy in non-apathetic patients at baseline.

The improvement of apathy in this cohort underlines the role of the dopaminergic system in the pathophysiology of apathy. The main change in our cohort, besides the evolution of the disease, was indeed the introduction of dopaminergic medication, which was identical in both groups of patients. The number of patients treated with antidepressant at last follow-up was the same that at baseline and could not account for the improvement of apathy. The post-hoc analysis on the effect of the dose of dopaminergic medication on the evolution of apathy was negative, indicating that the improvement of apathy by dopaminergic drugs was not dose-dependent. The occurrence of apathy after dopaminergic drugs reduction after subthalamic stimulation

Table 3 | Hyperdopaminergic behaviors

ASBPD	Baseline	Last visit	*p*-value	Effect size (CI 95%)
Nocturnal hyperactivity	0 [0–0]	0 [0–1]	<0.001	0.64 (0.34; 0.95)
Hypomania	0 [0–0]	0 [0–0]	0.64	0.09 (0.00; 0.39)
Psychotic symptoms	0 [0–0]	0 [0–1]	<0.001	0.62 (0.32; 0.93)
Eating behavior *N* = 85	0 [0–0]	0 [0–1]	<0.001	0.63 (0.32; 0.94)
Creativity *N* = 85	0 [0–0]	0 [0–0]	<0.001	0.57 (0.26; 0.88)
Hobbyism *N* = 85	0 [0–0]	0 [0–1]	<0.001	0.57 (0.26; 0.88)
Punding	0	0 [0–0]	0.02	0.37 (0.07; 0.67)
Risk taking behavior	0 [0–0]	0 [0–0]	0.33	0.21 (0.00; 0.51)
Compulsive shopping	0 [0–0]	0 [0–0]	0.02	0.50 (0.20; 0.80)
Pathological gambling *N* = 85	0	0 [0–0]	0.053	0.35 (0.05; 0.65)
Hypersexuality *N* = 85	0 [0–0]	0 [0–0]	0.22	0.25 (0.00; 0.55)
Dopaminergic addiction *N* = 85	0 [0–0]	0 [0–0]	0.64	0.09 (0.00; 0.39)
Appetitive functioning	0 [0–0]	0 [0–0]	<0.001	0.61 (0.30; 0.92)
Patients with ≥ 1 hyperdopaminergic behaviors *N* = 85	0 [0–0]	1 [0–1]	<0.001	0.92 (0.60; 1.23)

Median [interquartile range].

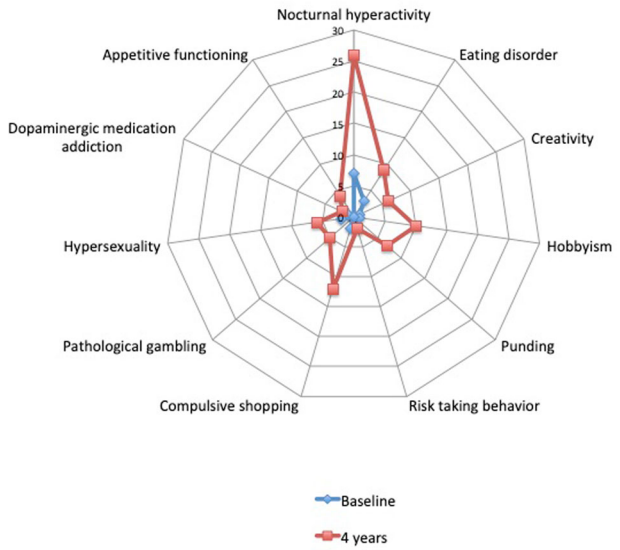

Fig. 2 | Evolution of hyperdopaminergic behaviors. Change of number of patients with hyperdopaminergic behaviors, according Ardouin Scale of Behavior in Parkinson's Disease.

was not dose-dependent, but driven by the degree of mesolimbic dopaminergic denervation[20]. The present study appears to contradict the 6-month pharmacological de novo PD study (in which apathetic de novo patients were randomized to rotigotine versus placebo for six months), which found an improvement of apathy in both active and placebo groups of around 60%. The marked and sustained improvement of apathy at six months under placebo was unexpected and per se an important result, highlighting the potential benefit coming from a non-pharmacological and multidisciplinary management of apathy. Non-pharmacological approaches, such as cognitive behavioral therapy, have been shown to be promising in anxiety and depression in PD[28,29], and are grounded on a solid framework also for apathy in PD[30].

The improvement of apathy in the long-term follow-up and not at 6 months might be related first to the insufficient dose of rotigotine in the randomized controlled study (maximal dose was fixed at 8 mg, corresponding to highest recommended dose in early PD), whereas in the present study there was no limit representing the routine care practice. Moreover, reverting apathy might take longer than 6 months. On top of that, dopaminergic sensitization for motivational behaviors might be higher in patients with apathy due to mesolimbic denervation, with the need for these patients of lower doses of dopaminergic medication in the same way to what happens for motor sensitization with greater dopaminergic denervation[9,10].

Other longitudinal studies in de novo PD found a stability[31,32] or a worsening[33–36] of apathy and neuropsychiatric symptoms at 4-5 years of follow-up. Methodological issues might explain this difference, such as different scales used to measure apathy[33,36]. Moreover, the prevalence of baseline apathy was lower in these studies (17% in the study of Weintraub and coll[36]), whereas in our population, such prevalence at baseline was of around 30%, which is considered to be representative of the prevalence of apathy in de novo PD[37].

Importantly we also found a significant improvement at 4 years of anxiety in the all group of patients, in line to other longitudinal studies[34,36].

A trend towards improvement of depression was also observed especially in the group of patients with baseline apathy, whereas other longitudinal studies found a slight worsening of depression at follow-up, probably because of methodological differences (scales, population)[32,34,36]. The improvement of anxiety independently of the presence of apathy at baseline and the lack of significant improvement of depression, possibly indicates specific, despite overlaps, anatomical, neurotransmission and functional alterations and suggests that grouping these three manifestations under a single umbrella of "hypodopaminergic triad" is over simplistic[19,38].

The impact of disease evolution on neuropsychiatric symptoms is complex, with higher prevalence at disease onset and at more advanced stages, as a consequence of fluctuations, dyskinesias, impulse control disorders, and axial dopa-resistant signs, such as cognitive decline. As already mentioned, apathy is a behavioral syndrome, in which motivational, emotional and cognitive dimensions can be recognized[13,39,40]. Whereas in more advanced disease, apathy more often reflects a cognitive decline and thus does not respond any longer to dopaminergic treatment[25], in early PD, it is more often isolated or associated to depression and anxiety, reflecting dopaminergic and serotonergic dysfunction and can be managed adjusting medical treatment.

In our cohort of early PD, patients presented mainly motivational and emotional apathy, without significant cognitive impairment after 4-year of disease evolution, explaining the ongoing improvement at last follow-up on dopaminergic treatment.

Conversely, an increase in the prevalence of cognitive impairment (defined as MOCA score < 26) of about 6% at 4 years has been found in the PPMI cohort[36]. This difference is probably related to our more restrictive inclusion criteria (MDRS ≥ 130), chosen in order to strictly select patients without cognitive apathy.

As expected, we found a worsening of non-motor symptoms, motor severity, and the onset of motor complications, although these remained mild at 4 years of follow-up. Fatigue significantly worsened with disease progression, similarly to what already described[34,36].

Interestingly, the group of patients with baseline apathy had higher scores of fatigue both at disease onset and at follow-up. De novo apathy has been found to be associated with fatigue and anhedonia[41]. Fatigue is a "catch-all symptom", used by patients to describe physical fatigue, or sleepiness, or a lack of energy or interest. Apathetic patients complain easily of fatigue. Thus, it is not surprising that apathetic patients at baseline had higher scores of fatigue. However, the lack of improvement of fatigue in this group with disease evolution, despite an improvement of apathy, suggests that different mechanisms than apathy also contribute to fatigue. The increase in fatigue with disease evolution in this study might be mainly related to the increase of diurnal sleepiness and to the worsening of motor symptoms.

On the other side, nocturnal hyperactivity and other so-called hyperdopaminergic behaviors significantly increased at 4 years. This is not

surprising since it has already been shown that impulsive compulsive behaviors are associated with dopaminergic treatment[42,43], with a prevalence in de novo PD similar to that in healthy controls, as shown in the PPMI cohort[44]. Apathy has been hypothesized to be a risk factor for the development of ICB, because associated to a more severe mesocorticolimbic denervation, in analogy to akinesia, reflecting more severe nigrostriatal denervation, being a risk factor for dyskinesias[19]. However, here, the worsening of ICB and of nocturnal hyperactivity was not different in apathetic and non-apathetic patients. Nevertheless, in a post-hoc analysis of the PPMI cohort, apathy was indeed predictive of the occurrence of ICB[45]. Recently, Theis et al. found that both apathy and DRD3 polymorphysm were risk factors for ICB in early PD[46]. In our study, baseline apathy was not associated with higher occurrence of ICB. However, our population was underpowered to detect such a difference and the duration of follow up was probably too short.

Diurnal sleepiness also worsened with disease progression, probably favored by nocturnal hyperactivity in this cohort of patients, whereas it is infrequent in de novo PD[47].

Concerning neuropsychiatric fluctuations, these were more common at 4 years of follow-up, as expected with disease progression[48,49]. Interestingly, we observed greater frequency of neuropsychiatric off than on (30% versus 10%). This could be related to a recall bias, with neuropsychiatric OFF more easily recognized and retrospectively recalled by patients, as more distressful, whereas neuropsychiatric ON are more pleasant and therefore more egosyntonic.

Despite the improvement of apathy and neuropsychiatric symptoms, quality of life significantly worsened at 4 years, with a worsening in all domains but the emotional well-being domain, which was improved. Overall, patients with baseline apathy had worse quality of life at baseline and at follow-up compared to non-apathetic ones, despite the improvement of apathy. Quality of life relies on multiple factors. In our cohort, the worsening of quality of life was probably mainly driven by the worsening of motor symptoms, and non-motor non-neuropsychiatric symptoms. This finding, although unexpected, supports the recent criticism to the old concept of "honeymoon"[50], with several motor and non motor aspects, which can hamper quality of life also in early PD. The worsening in cognitive domain is not reflected by a worsening in cognitive functions. In routine care, it is not rare to have a mismatch between their judgment on cognition and the real performance on test[51,52]. This might be related to the lack of sensitivity for mild impairment of cognitive test. Furthermore, in PD mood disorders can participate to this subjective cognitive complain[53]. The improvement in emotional well-being domain can be explained by the improvement of apathy and it goes along with the improvement in communication domain in the apathetic group, which is probably related to an emotional, a motivational and cognitive "awakening" induced by dopaminergic medication. From a neuropsychiatric point of view, patients under dopaminergic medication can become talkative, with a spectrum reaching in some logorrhea and flight of ideas, and this goes along with a reduction in bradyphrenia[48,54].

Our study has several limitations, first of all its sample size, which can restrain its power.

Its pharmacological nature did not allow to address potential non-pharmacological factors, which might have contributed to apathy improvement, such as cognitive-behavioral therapy or life-style change, which should be explored in the future.

Furthermore, we did not use objective measures of sleep, since the study of sleep and sleepiness was out the scope of our study. However, implementing future studies with these objective measures might be useful, in order to better define the sleep profile in early PD.

In conclusion, we showed a change in the emotional profile in a selected population of de novo PD patients without cognitive decline, with an improvement of motivational apathy and other neuropsychiatric symptoms along with an increase of hyperdopaminergic behaviors after the introduction of dopaminergic treatment. Our findings point out the need of a sustained exposure to dopaminergic treatment in order to achieve this improvement.

Methods

Study design and participants

This is a prospective multicenter French study of a cohort of de novo PD followed up for 3 to 5 years.

Patients were initially included in the honeymoon study (NCT02786667), a large observational study on neuropsychiatric symptoms, if: aged between 30 and 72 years; had a diagnosis of PD for < 2 years; with no cognitive impairment (defined as a score on the MATTIS Dementia rating scale (MDRS) < 130/144 or on Frontal assessment battery (FAB) < 15/18); no dopaminergic treatment; no active comorbidity of major psychiatric disease (no suicidal risk, no major depressive episode according to DSM IV, no active psychosis). Patients under rasagiline or antidepressant could be included provided that the treatment was stable for the last 3 months before inclusion. 198 patients were enrolled in the Honeymoon study. Within this cohort, apathetic de novo patients were enrolled in a 6-month randomized controlled study assessing rotigotine versus placebo on apathy improvement[24].

The current study assessed 90 patients, initially included in the honeymoon study and followed up for 3 to 5 years (NCT03141944): 60 patients who did not present apathy at baseline, 30 patients who were apathetic at baseline (according to a score of the baseline Lille Apathy Rating Scale ≥ −21). Patients involved in the current study were required to have a confirmed diagnosis of PD, to be on dopaminergic treatment, and to have a MDRS ≥ 130.

Approval from Ethical Committee (Comité de Protection des Personnes Sud Est V) was obtained for both studies (CPP 11-CHUG-13 and 16-CHUG-23). The study was performed in accordance with the Declaration of Helsinki and all patients signed an informed consent.

Assessment

At both baseline and follow-up visit, patients underwent a motor assessment using the MDS-UPDRS[55], as well as a thorough neuropsychological assessment. This included the Starkstein apathy scale for apathy (range 0–42)[56], the Beck depression inventory-2 (BDI-2) for depression (range 0–63)[57], the State-Trait Anxiety Inventory for anxiety trait (STAI-trait) and state (STAI-state)[58], each ranging from 20 to 80, the Ardouin Scale of Behavior in Parkinson's Disease (ASBPD) for apathy, anxiety, depression (each item ranging 0–4), hyperdopaminergic behaviors, and non-motor-fluctuations[59], the PFS-16 for the fatigue[60], the MATTIS Dementia rating scale (range 0–144)[61] and the Frontal Assessment Battery (FAB, range 0–18) for cognition[62]. Quality of life was evaluated by PDQ-39 (the summary index (PDQ-39 SI) was calculated by the sum of dimension total scores divided by 8)[63].

Dopaminergic treatment was converted to levodopa equivalent dose, according to Jost et al. 2023[64].

Outcome measures

The primary outcome of the study was the evolution of the apathy between baseline and follow-up visit, measured as the change in the Starkstein apathy scale. We chose the Starsktein apathy scale in this longitudinal study, instead of the Lille apathy scale[65] used in the honeymoon study[24], because it appears to be more sensitive to motivational apathy and to the behavioral changes following dopaminergic medication adjustment, whether the latter is more sensitive to cognitive apathy.

As secondary outcomes, we assessed the evolution over 3–5 years of: depression, measured with BDI-2; anxiety, measured with STAI state (measuring the anxiety in that precise moment) and trait (measuring long-standing anxiety); fatigue, measured with the PFS-16; hyperdopaminergic behaviors, as well as non-motor neuropsychiatric fluctuations measured with the ASBPD and quality of life, measured with the PDQ-39.

Hyperdopaminergic behaviors were assessed using ASBPD. Nocturnal hyperactivity, hypomanic mood, psychotic symptoms, punding, pathological gambling, hypersexuality, dopaminergic addiction were considered as

pathological if the score in the respective item of the ASBPD was ≥ 1. Cut-off score for clinically relevant hyperdopaminergic compulsive shopping was defined as > 1 for men and > 2 for women. A patient was considered affected by clinically relevant hyperdopaminergic eating behavioral issues, creativity, hobbyism, risk taking behavior, appetitive behavior whenever her/his score in the respective item of the ASBPD was ≥ 2. This cut off is based on general population normative data of the ASBPD (unpublished data).

The impact of dopaminergic medication in the change of primary and secondary outcomes was explored as well.

Statistical analysis

Data were given as number and frequency for categorical variable, mean and standard deviation for normally distributed variables (tested with a Shapiro-Wilk test), median and interquartile range (IQR) for non-normally distributed variables. Comparisons were realized using a paired t-test, when the distribution was normal, otherwise with a Wilcoxon signed rank test. For categorical variables, a McNemar test was used.

For primary outcome, a paired t-test was used.

For secondary outcomes, a repeated measure ANOVA was realized using the factor apathy (a patient was considered apathetic whenever the score at the Starkstein apathy scale was ≥ 14). The procedure of Benjamini-Hocheberg was used for correcting for multiple comparisons across all tests (including primary and secondary outcome). The Cohen effect size and confidence interval were calculated for the paired test. Statistically significance was set to $p < 0.05$.

A post-hoc analysis with a mixed model REML was realized, using the total levodopa daily equivalent dose as well as the dopamine agonists dose expressed as levodopa equivalent dose.

The sample size was calculated (paired difference test) in order to show a statistically significant difference of 1,8 point with 80% of power, of 2 points with a power of 90% (considering the Starkstein apathy scale at 11.6 + /−5.9 and alpha risk of 0.05 (logiciel nQuery Advisor 7.0 -)[66].

Data availability

Anonymized data of this study will be available from the corresponding author on reasonable request from any qualified researcher, following the EU General Data Protection Regulation.

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Author contributions

A.C.: Study Design, Data collection and interpretation, Draft writing and revision. E.S., E.L., A.B., S.T., P.K.: Study Design, Data collection, manuscript revision. D.S.: Data analysis and interpretation, manuscript revision. M.A., S.M., H.K., C.T., V.F., E.M., P.P.: data collection and interpretation, manuscript revision.

Competing interests

A.C. received a research grant from Medtronic (to the institution), reimbusement for scientific meetings from ABBVIE, honoraria for lectures from MDS and ABBVIE, M.A.: Abbvie, Merz, Aguettant, Biogen Pharmaceuticals, Ipsen Pharma, Linde, Ever Pharma, Medtronic. S.M. received research grant support from Medtronic, Newronika, Grenoble

Alpes University, Huntington's Disease Network. V.F.: Consultancy fees from AbbVie France, Honorarium from MEDTRONIC. C.T.: AbbVie, IPSEN, Lynde. E.M. is an associated editor of npj Parkinsońs Disease. E.M. has received honoraria from Medtronic for consulting services. She has also received restricted research grants from the Grenoble Alpes University, France Parkinson, IPSEN and Abbott. S.T. received grant from ANR, Neuratris, Boston Scientific, personal fees for conferences from Merz, Aguettant, NHC, for board/consulting from ABBVIE, Medtronic, Boston Scientific, for meetings from MDS and ABBVIE. P.K.: reports research or educational grants from Swiss National Science Foundation, ROGER DE SPOELBERCH Foundation, Fondation Louis-Jeantet, Carigest, Institut National de la Santé et de la Recherche Médicale, France Parkinson, Edmond Safra Philantropic Foundation, Bertarelli Foundation, Annemarie Opprecht Foundation, Parkinson Schweiz, Michael J Fox Foundation, Aleva Neurotherapeutics, Boston Scientific, Medtronic, St. Jude Medical, GE Healthcare, Idorsia, UCB, all paid to employing institutions; lecturing fees to employing institution from Boston Scientific, Bial, Advisis; travel expenses to scientific meetings from Boston Scientific, Zambon, Abbvie, Merz Pharma (Schweiz) AG. E.S., H.K., E.L., A.B., D.S., P.P.: declare no competing interests.

Additional information

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