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Jean-François Houvenaghel[a,b*1], Sophie Drapier[a,b], Joan Duprez[a], Gabriel Hadrien Robert[a,c], Audrey Riou[a,b], Dominique Drapier[a,c], Paul Sauleau[a,d], Marc Vérin[a,b]

[a] "Behavior and Basal Ganglia" research unit (EA 4712), University of Rennes 1, Rennes, France

[b] Department of Neurology, Rennes University Hospital, Rennes, France

[c] Department of Psychiatry, Rennes University Hospital, Rennes, France

[d] Department of Neurophysiology, Rennes University Hospital, Rennes, France

[1] **Corresponding author**: Jean-François Houvenaghel, Service de Neurologie, CHU Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes Cedex, France. Phone: +(33)2 99 28 98 42, Fax: +(33)2 99 28 41 32, E-mail: jeanfrancois.houvenaghel@chu-rennes.fr

ABSTRACT

Introduction: Treatment optimization using continuous subcutaneous apomorphine infusion (CSAI) improves the control of motor fluctuations of patients with Parkinson's disease (PD). Although CSAI seems to be cognitively and behaviorally safe and to improve the quality of life, very few studies have investigated its influence in these domains, especially in patients without cognitive impairment. Methods: We estimated the impact of CSAI on motor symptoms, cognition, psychiatric domains and quality of life in parkinsonian patients without cognitive impairment by comparing the scores of 22 patients assessed before and 6 months after the start of add-on CSAI. Results: Optimized treatment with CSAI was associated with i) reduced motor fluctuations, ii) unchanged cognition, iii) unchanged psychiatric domains, and iv) improved quality of life in physical and psychological aspects. Conclusion: In PD patients without cognitive impairment, CSAI improves motor symptoms and quality of life and, as suggested by previous studies, alters neither cognition nor mental health.

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1 INTRODUCTION

The addition of continuous subcutaneous apomorphine infusion (CSAI) to oral antiparkinsonian medication is considered to be an effective treatment for motor symptoms of patients with Parkinson's disease (PD) who are severely disabled by dyskinesia and/or motor fluctuations (for a review, see [1,2]). A randomized placebo-controlled study confirmed recently this widely accepted view [3]. CSAI is frequently considered to be cognitively safe, or even to have a potentially beneficial effect on cognition [4–6]. However, to our knowledge, very few studies have investigated these cognitive aspects with neuropsychological batteries, and most of them had small and heterogeneous patient samples [7–14]. The two studies that have so far been conducted in patients without severe cognitive impairment, as indicated by the fact that they were not contraindicated for subthalamic nucleus deep brain stimulation (STN-DBS), did not report any significant CSAI-induced changes [7,8,10]. In one study, executive, episodic verbal memory, and visuoperceptual performances remained stable in all seven patients 6 and 12 months after the introduction of CSAI [7]. In the other study, there was no significant change in either episodic verbal memory or visual working memory at 12 months for thirteen patients [10], or at 40 months for two patients [8]. However, since the exclusion criteria for STN-DBS rely on motor and/or neuropsychological symptom severity, we cannot know whether the patients in these studies had cognitive impairment. Similar results have been reported for patients with advanced PD who had more important motor and/or neuropsychological symptoms, and therefore underwent apomorphine infusion as an alternative therapeutic strategy [9,11,13,14]. A study evaluating the effect of 12 months of treatment in 23 patients found that executive functions were unaffected by CSAI, although a slight cognitive slowdown was observed, presumably induced by disease progression [11]. Similarly, a recent study failed to find any significant modulation of either overall cognitive efficiency (Mini-Mental State Examination, MMSE) or overall executive efficiency (Frontal

Assessment Battery, FAB, or Scales for Outcomes in Parkinson's Disease-Cognition, SCOPA-COG) after a median follow-up duration of 26 months in 7-24 patients with cognitive disorders [13,14]. Lastly, one study reported a slight executive improvement in 12 patients after 6 months of add-on CSAI [9]. Thus, even if CSAI has frequently been reported to be cognitively safe, further evidence from neuropsychological assessments is needed, especially in patients with no cognitive impairment, who represent more than 50% of all patients with PD [15].

In addition, research interest in quality of life is very recent, with only four studies published in international journals, all concerning patients with advanced PD [9,16–18]. Two of these reported a significant improvement in total scores on the Parkinson's Disease Questionnaire (PDQ-8; PDQ-39) [16,18], which was specifically built for PD, while a third found a trend towards an improvement [9]. The last one did not shown significant changes [17].

In this context, we conducted a retrospective study to investigate the influence of 6 months of add-on CSAI on the cognitive, motor and psychiatric domains, as well as on quality of life, in patients with no cognitive impairment at baseline. We hypothesized that add-on CSAI reduces motor symptoms and improves quality of life without disturbing cognitive or psychiatric aspects.

2 METHODS

2.1 Participants

During the 2006-2015 period, the add-on CSAI treatment was introduced in 122 patients diagnosed with idiopathic PD according to the UK Brain Bank criteria at Rennes University Hospital. Among those 122 patients, 44 underwent motor and neuropsychological assessments before (baseline; M0) and 6 months (M6) after continuous add-on CSAI. Patients with dementia or mild cognitive impairment were excluded on the basis of the Level 1

diagnostic criteria recommended by the Movement Disorders Society [19], and the Mattis Dementia Rating Scale (MDRS; score > 137 [20] at baseline). Totally, 22 patients were included (8 men, 14 women) (Table 2). In addition to motor and neuropsychological assessments, most of them underwent psychiatric and quality-of-life assessments. Patients underwent the full assessment within the same week. All the patients were evaluated on dopaminergic medication both at baseline and during the follow-up assessments. At baseline, medication included both dopamine agonists and levodopa therapy in 21 patients, and levodopa alone in one patient. The study was approved by the local ethics committee of Rennes University Hospital and conducted in accordance with the Declaration of Helsinki and current French legislation.

2.2 Motor assessment

Disease severity was rated on the Unified Parkinson's Disease Rating Scale (UPDRS-II, III and IV), and the Hoehn and Yahr and Schwab and England scales.

2.3 Neuropsychological assessment

In addition to the MDRS, we administered a neuropsychological battery that mainly investigated executive functioning. This battery included the phonemic (letter *p*) and semantic (animals) verbal fluency tasks (2-min version), the Nelson's simplified version of the Wisconsin Card Sorting Test (MCST), the Trail Making Test (TMT) and the Golden's version of the Stroop Interference Test.

2.4 Psychiatric assessment

Apathy, depression and anxiety were assessed by an experienced psychiatrist using the Apathy Evaluation Scale (AES), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the AMDP-AT anxiety scale.

2.5 Quality-of-life assessment

Quality of life was assessed with the 36-item Short-Form Survey (SF-36), the 39-item PDQ (PDQ-39) and the Clinical Global Impression Improvement (CGI-I) scale.

2.6 Statistical analyses

Changes in dopaminergic treatment and motor, psychiatric, neuropsychological, and quality-of-life scores following add-on CSAI were compared using the Wilcoxon matched-pairs test. The significance threshold was set at $p = 0.05$ for all analyses. We did not correct the level of significance for multiple comparisons given the exploratory nature of our study to reduce the risk of type II error. However, we were mindful of the consecutively higher probability of a type 1 error.

3 RESULTS

3.1 Treatments

The introduction of add-on CSAI was associated with a significant reduction in levodopa treatment of 38% (-312 ± 312 mg/d, $p = 0.0004$) and an increase in the total levodopa equivalent daily dose (LEDD) of 45% (392 ± 382 mg/d, $p = 0.0004$) (Table 1). At 6 months, the apomorphine treatment represented 55% of total LEDD. Daytime CSAI had a mean duration of 15.4 ± 2.1 hours (range: 13-24) at a mean hourly rate of 4.7 ± 1.0 mg (range: 3.5–7) and a mean bolus number of 2.0 ± 1.8 per day (range: 0-5), with a mean dose of 2.9 ± 1.2 mg (range: 0–5) per bolus.

Table 1: Levodopa equivalent daily dose (mean ± *SD*) of patients with PD before (M0) and after 6 months (M6) of add-on CSAI

	N	M0	M6	M6 - M0	*p* value
Dopamine agonists (mg/day)	22/22	278.7 ± 147.5	244.7 ± 146.8	-34.1 ± 86.9	0.11

L-DOPA (mg/day)	**22/22**	**791.7 ± 409.7**	**479.5 ± 381.6**	**-312.1 ± 312.7**	**< 0.001**
Total apomorphine dose (mg/day)	22/22		754.0 ± 209.7		
Total LEDD (mg/day)	**22/22**	**1087.7 ± 485.5**	**1478.6 ± 552.7**	**391.9 ± 381.9**	**< 0.001**

Note. LEDD = levodopa equivalent daily dose; *SD* = standard deviation.

3.2. Motor assessment

Add-on CSAI significantly reduced motor fluctuations, as shown by the decrease in the UPDRS-IV Fluctuations score (sum of Items 36-39), which improved by -1.04 ± 1.8 points (p = 0.005). No other significant motor improvement was observed. In parallel, we observed a trend towards an increase in the UPDRS-III ON medication score (non-dopaminergic symptoms; p = 0.09) and the Schwab & England OFF medication score (p = 0.09), indicating potential disease progression (Table 2).

Table 2: Motor assessments (mean ± *SD*) of patients with PD before (M0) and after 6 months of add-on CSAI

	N	M0	M6	M6 - M0	*p* value
Sex (M:F)		8:14			
Age (years)		57.5 ± 9.6			
Disease duration (years)		11.1 ± 4.4			
Side of symptom onset (R:L)		12:10			
Education (years)		11.4 ± 4.0			
UPDRS-II ON med	22/22	5.9 ± 4.2	6.4 ± 5.3	0.48 ± 6.8	0.74
UPDRS-II OFF med	22/22	17.9 ± 7.5	17.4 ± 4.8	-0.5 ± 7.3	0.82
UPDRS-III ON med	21/22	11.1 ± 8.1	14.5 ± 8.9	3.4 ± 9.1	0.09
UPDRS-III OFF med	20/22	37.7 ± 16.8	40.2 ± 14.7	2.5 ± 14.6	0.57
UPDRS-IV	22/22				
Total score		7.0 ± 3.3	5.8 ± 2.6	-1.2 ± 3.1	0.11
Dyskinesia		2.7 ± 2.4	2.3 ± 1.8	-0.4 ± 2.2	0.30
Fluctuations		**3.4 ± 1.2**	**2.4 ± 1.4**	**-1.0 ± 1.8**	**0.005**
Hoehn & Yahr ON med	21/22	1.4 ± 0.9	1.1 ± 0.9	-0.3 ± 0.9	0.16
Hoehn & Yahr OFF med	21/22	2.3 ± 1.0	2.3 ± 0.8	-0.0 ± 0.8	0.86
Schwab & England ON med (%)	21/22	91.9 ± 6.8	91.4 ± 7.9	-0.5 ± 7.4	0.78
Schwab & England OFF med (%)	21/22	73.8 ± 16.3	66.2 ± 23.8	-7.6 ± 18.4	0.09

Note. *SD* = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

3.3. Neuropsychological assessment

Very few cognitive changes were observed at 6 months. Patients showed a slight slowdown, as measured by the Stroop Word score ($p = 0.04$). However, this slowdown was not reflected in the other scores, such as the Stroop Colour score ($p = 0.37$), or the TMT Part A which, on the contrary, tended to be faster ($p = 0.10$). The Stroop interference score also tended to be better at 6 months ($p = 0.10$) (Table 3).

Table 3: Neuropsychological assessment (mean ± *SD*) of patients with PD before (M0) and after 6 months of add-on CSAI

	N	M0	M6	M6 - M0	*p* value
MDRS	22/22				
Attention		36.6 ± 0.7	36.6 ± 0.5	0.0 ± 0.7	1.00
Initiation		36.2 ± 1.4	36.1 ± 1.6	-0.1 ± 1.8	0.66
Construction		5.9 ± 0.2	6.0 ± 0.0	0.1 ± 0.2	1.00
Conceptualization		37.9 ± 1.3	38.3 ± 1.2	0.4 ± 0.9	0.11
Memory		24.1 ± 0.6	24.3 ± 1.0	0.2 ± 1.1	0.50
Total		140.8 ± 2.0	141.3 ± 2.5	0.5 ± 2.2	0.18
Stroop	22/22				
Word		**97.3 ± 17.3**	**93.8 ± 17.2**	**-3.5 ± 12.3**	**0.04**
Colour		69.4 ± 12.5	67.8 ± 13.3	-1.6 ± 9.5	0.37
Colour-Word		35.1 ± 9.6	37.1 ± 11.1	2.0 ± 8.0	0.18
Interference		-5.3 ± 7.4	-1.9 ± 6.8	3.3 ± 8.3	0.10
TMT	22/22				
Errors A		0.18 ± 0.4	0.09 ± 0.3	-0.10 ± 0.5	0.46
Time A (s)		42.1 ± 14.7	39.8 ± 15.9	-2.3 ± 8.3	0.10
Errors B		0.45 ± 0.9	0.32 ± 0.65	-0.14 ± 1.1	0.65
Time B (s)		91.6 ± 32.2	86.4 ± 41.6	-5.2 ± 36.1	0.27
TMT B-A (s)		49.5 ± 26.2	46.6 ± 32.5	-2.9 ± 34.1	0.42
Semantic Fluency	21/22	32.6 ± 7.0	33.5 ± 8.5	0.9 ± 5.5	0.37
Phonemic Fluency	20/22	20.5 ± 6.2	21.8 ± 5.8	1.3 ± 4.1	0.16
WCST	21/22				
Categories		5.3 ± 1.3	5.4 ± 1.3	0.1 ± 0.9	0.46
Errors		5.5 ± 7.0	4.9 ± 7.8	-0.5 ± 4.1	0.57
Perseverations		1.9 ± 2.8	1.9 ± 3.6	-0,1 ± 2.2	0.67

Time (s)		206.0 ± 73.1	200.0 ± 81.8	-5.9 ± 57.0	0.58
UPDRS I	22/22	1.75 ± 1.4	1.9 ± 2.0	0.1 ± 1.4	0.56
MADRS	13/22	5.1 ± 4.6	5.4 ± 5.0	0.31 ± 4.7	0.65
AMDPAT	10/22	9.1 ± 5.7	7.5 ± 5.5	-1.6 ± 5.0	0.48
AES	10/22	28.5 ± 7.2	30.1 ± 9.6	1.6 ± 5.2	0.27

Note. *SD* = standard deviation; TMT: Trail Making Test; MCST = Modified Wisconsin Card Sorting Test; MDRS = Mattis Dementia Rating Scale; UPDRS-I = Unified Parkinson's Disease Rating Scale Part I; MADRS = Montgomery and Åsberg Depression Rating Scale; AMDPAT = AMDP-AT anxiety scale; AES = Apathy Evaluation Scale.

3.4. Psychiatric assessment

At 6 months follow up, no significant modification was observed in overall psychiatric aspects (UPDRS-I), depression (MADRS), apathy (AES) or anxiety (AMDP-AT), despite missing data for the three last scales, owing to the retrospective status of our study (Table 3). Of the 22 patients, one patient developed impulse control disorders (sexual compulsion and compulsive shopping) and another presented slight simple visual hallucinations. Both events disappeared when the dopamine agonist treatment was reduced without any change in CSAI treatment.

3.5. Quality-of-life assessment

The overall quality of life tended to improve, according to the total score of the SF-36 (p = 0.09). When we explored the subscores, we observed that the add-on CSAI treatment improved physical domains, which were the most impaired at baseline, but also improved psychological domains. The improvement in the physical composite subscore (9.7% ± 13.9, p = 0.01) was sustained by a significant improvement in the bodily pain subscore (13.9% ± 20.5, p = 0.02) and a trend towards an improvement in the role physical subscore (20.6% ± 40.7, p = 0.06). In addition, we found a significant reduction in the bodily discomfort subscore of the PDQ-39 (9.2% ± 14.4, p = 0.01). The psychological improvement was related

to both a significant decrease in the stigma subscore of the PDQ-39 (10.9% ± 20.5, $p = 0.01$) and a trend towards an improvement in the social functioning subscore of the SF-36 (9.0% ± 23.4, $p = 0.10$). Finally, at 6-month follow up, the mean CGI-I score was 66.4% ± 16.0 (Table 4).

Table 4: Quality-of-life assessment (mean ± *SD*) of patients with PD before (M0) and after 6 months of add-on CSAI

	N	M0	M6	M6 - M0	*p* value
SF 36 (%)					
General Health Perception	17/22	46.8 ± 18.2	49.1 ± 19.3	2.3 ± 7.7	0.26
Physical Function	17/22	66.2 ± 23.7	64.7 ± 25.6	-1.5 ± 15.5	0.53
Role Limitations Because of Physical Health Problems	17/22	32.3 ± 31.6	52.9 ± 39.4	20.6 ± 40.7	0.06
Role Limitations Because of Emotional Problems	17/22	70.6 ± 35.1	68.6 ± 39.9	-2.0 ± 39.9	0.76
Social Function	18/22	54.9 ± 18.8	63.9 ± 19.6	9.0 ± 23.4	0.10
Bodily Pain	**18/22**	**45.6 ± 23.3**	**59.4 ± 20.9**	**13.9 ± 20.5**	**0.02**
Mental Health	18/22	64.4 ± 14.1	66.7 ± 11.1	2.2 ± 11.8	0.50
Vitality	18/22	44.7 ± 19.5	51.1 ± 15.1	6.4 ± 17.6	0.20
Mental Composite Score	17/22	59.4 ± 14.8	62.0 ± 17.3	2.6 ± 14.7	0.43
Physical Composite Score	**16/22**	**45.6 ± 15.7**	**55.3 ± 19.4**	**9.7 ± 13.8**	**0.01**
Total	16/22	52.0 ± 13.9	58.4 ± 17.5	6.4 ± 13.1	0.09
PDQ-39 (%)					
Mobility	19/22	38.8 ± 19.6	35.4 ± 19.9	-3.4 ± 13.4	0.19
Activities of daily living	19/22	30.5 ± 19.9	28.3 ± 14.7	-2.2 ± 16.6	0.42
Emotional wellbeing	19/22	35.5 ± 20.2	32.9 ± 20.3	-2.6 ± 15.7	0.48
Stigma	**19/22**	**35.2 ± 30.3**	**24.3 ± 21.4**	**-10.9 ± 20.5**	**0.03**
Social Support	18/22	11.6 ± 15.2	13.9 ± 20.2	2.3 ± 8.0	0.46
Cognitions	18/22	27.4 ± 23.1	28.1 ± 21.7	0.7 ± 11.7	0.75
Communication	18/22	24.1 ± 19.1	22.0 ± 10.4	2.3 ± 12.1	0.36
Bodily Discomfort	**19/22**	**52.2 ± 14.1**	**43.0 ± 17.2**	**-9.2 ± 14.4**	**0.01**
Total	18/22	30.4 ± 10.6	28.5 ± 12.6	-1.9 ± 6.9	0.27
CGI-I (%)	22/22		66.4 ± 16.0		

Note. *SD* = standard deviation; SF-36 = 36-Item Short Form Survey; PDQ-39 = 39-item Parkinson's Disease Questionnaire; CGI-I = Clinical Global Impression Improvement scale.

4 DISCUSSION

In the present study, we investigated for the first time the influence of 6 months of treatment optimized with add-on CSAI on motor symptoms, cognitive and psychiatric domains, and quality of life in 22 PD patients without cognitive impairment. The add-on CSAI was associated with i) reduced motor fluctuations, ii) no change in cognition, iii) no change in psychiatric domains, and iv) improved quality of life in physical and psychological aspects. The overall results of the current study are in line with previous observations realized in more advanced patients, indicating that add-on CSAI improves motor symptoms and quality of life without altering cognition or inducing psychiatric symptoms [7–12,14,17].

The main result for motor function was a significant reduction in the motor fluctuation score, confirming that add-on CSAI is efficient in this motor aspect [11,21]. This improvement probably resulted from both the reduction in pulsatile levodopa treatments and the increase in total LEDD through the introduction of the apomorphine infusion, although a specific role of the apomorphine molecule cannot be ruled out.

As expected, cognitive functioning, as assessed with neuropsychological tools, was not disturbed when we compared the same patients without cognitive deterioration at baseline and 6 months after the introduction of add-on CSAI. Our results confirm the absence of cognitive change reported in previous observations for smaller samples with greater variations in cognitive severity [7–11,13,14]. The only significant change that we found was a reduction in the number of words correctly read during 45 seconds in the Stroop Word Test. This reduction may suggest that add-on CSAI induces some degree of slowdown, as reported in patients with a more severe disease [11]. However, unlike the study by Drapier et al. (2012), this slowdown was not confirmed by other cognitive indices, such as colour naming accuracy or the time taken to complete the TMT Part A, which actually tended to be shorter at 6 months [11]. However, in another study using more sensitive tools to evaluate cognitive action control

we did not found any significant change [22] . Overall, add-on CSAI appears to be cognitively safe in PD patients with no cognitive deterioration.

Furthermore, we did not find any change in depression, anxiety or apathy scores following introduction of add-on CSAI, despite the frequency of these symptoms in PD [15]. Although these results should be interpreted with caution, as many data were lacking owing to the retrospective design of our study, they are nonetheless in line with previous studies demonstrating either psychiatric safety in patients with PD who are cognitively normal or mildly cognitively impaired [7,10,12], or an improvement in apathy [9,17,18] or anxiety [16] among patients with a more severe disease. In addition, impulse control disorders and simple visual hallucinations noted in two different patients both vanished when the oral dopamine agonist treatment was reduced, without the need to change the CSAI. Once again, the add-on CSAI treatment seems to be psychiatrically safe in this population, but these two cases demonstrate that further studies are needed to establish the optimum medical treatment to be associated with CSAI.

Finally, quality of life improved with add-on CSAI on some domains but not on the total score. Surprisingly, only two studies reported a significant improvement in total scores on the PDQ [16,18], while a third found a trend towards an improvement [9], and another no significant change [17]. The absence of change on the total score in our cohort probably reflected the fact that our patients had a generally better quality of life at baseline than those in the above-mentioned studies [9,16,18]. This may have induced a floor effect for the improvement following add-on CSAI. In this respect, we highly recommend to use the full PDQ-39 questionnaire, rather than its abbreviated version, to study the influence of add-on CSAI in patients with mild-to-moderate disease severity. When we explored the subscores of the quality-of-life questionnaires, we found specific improvements in physical aspects such as bodily discomfort and bodily pain, and a trend towards an improvement in role limitations

because of physical health problems. We also observed an improvement in psychological domains such as stigma. This psychological improvement was only described in one [16] of the two studies that investigated this domain, both in advanced PD [9]. This improvement is very important, as felt stigma is very frequent in patients with PD, and reflects psychological distress [23]. Add-on CSAI treatment therefore induced a motor benefit, but also led to an improvement in psychological aspects.

Several points need to be kept in mind when interpreting our results. The first limitation of our study is that it is a retrospective one. Further, some data were missing and we had no control group with an optimized oral medical treatment. Thus, we cannot say whether the absence of significant change resulted from a lack of statistical power or from a real absence of effect. However, this study provides important empirical evidence regarding the influence of CSAI on nonmotor domains and quality of life in PD. Similarly, we cannot rule out the possibility that the beneficial effect measured on self-report questionnaires was, at least in part, induced by placebo or care effects. In the same way, we cannot exclude that the lack of significant changes in the neuropsychological tests was due to practice effects. However, in a control group, we only observed negligible practice effects at 6-month follow-up (only one score was significantly better at 6 months; see supplementary data). In addition, mild cognitive impairment was excluded on the basis of the Level 1 diagnostic criteria recommended by the Movement Disorders Society [19], so further studies using the more sensitive Level 2 diagnostic criteria are needed to confirm our results. Moreover, our study design estimated the influence of the overall change in antiparkinsonian treatment, rather than the specific role of the apomorphine molecule, its continuous delivery or the impact of the levodopa reduction following the start of CSAI. Finally, the present study is the first to focus on the influence of add-on CSAI treatment according to neuropsychological status at baseline.

Other studies are needed to confirm and complete our results, notably by adding nonexecutive tasks, as recommended by the MDS task force [19], as well as a nonmotor symptoms scale such as the NMSS.

Conclusion

The goal of the present study was to describe for the first time the effects of CSAI in the motor, cognitive, and psychiatric domains, as well as on quality of life, in patients with PD who had no cognitive disorders. Our results indicate that CSAI has a beneficial effect on motor fluctuations and quality of life, without any deleterious impact on the cognitive or psychiatric domains. Although further studies are needed to confirm and complete these results, notably in patients with more impaired cognitive profiles, the current study argues in favour of the overall cognitive and psychiatric safety of CSAI in patients with PD.

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Compliance with ethical standards

Conflicts of interest: Dr Sophie Drapier received speech honorarium from Teva and Medtronic and served on scientific advisory boards for Aguettant and Britannia. Pr Marc

Vérin has served on the Scientific Advisory Board for Aguettant and Orkyn and received speech honorarium from Teva and Medtronic.

Ethical standards: This study was approved by the ethics committee of Rennes University Hospital and conducted in accordance with the Declaration of Helsinki and current French legislation (Huriet Act).

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