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1 **Effects of continuous subcutaneous apomorphine infusion in**
2 **Parkinson's disease without cognitive impairment on motor,**
3 **cognitive, psychiatric symptoms and quality of life**
4

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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.

Wordcount: Abstract: 151 - Main text: 3092. 23 references, 4 tables, no figures, 1 supplemental data.

1 **1 INTRODUCTION**

2

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

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

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

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

18 **2 METHODS**

19

20 **2.1 Participants**

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

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

11 **2.2 Motor assessment**

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

14 **2.3 Neuropsychological assessment**

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

20 **2.4 Psychiatric assessment**

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

1 2.5 Quality-of-life assessment

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

4 2.6 Statistical analyses

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

11 3 RESULTS

12 3.1 Treatments

13 The introduction of add-on CSAI was associated with a significant reduction in levodopa
14 treatment of 38% (-312 ± 312 mg/d, $p = 0.0004$) and an increase in the total levodopa
15 equivalent daily dose (LEDD) of 45% (392 ± 382 mg/d, $p = 0.0004$) (Table 1). At 6 months,
16 the apomorphine treatment represented 55% of total LEDD. Daytime CSAI had a mean
17 duration of 15.4 ± 2.1 hours (range: 13-24) at a mean hourly rate of 4.7 ± 1.0 mg (range: 3.5–
18 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
19 mg (range: 0–5) per bolus.

20
21 **Table 1:** Levodopa equivalent daily dose (mean \pm SD) of patients with PD before (M0) and
22 after 6 months (M6) of add-on CSAI

	<i>N</i>	M0	M6	M6 - M0	<i>p</i> value
Dopamine agonists (mg/day)	22/22	278.7 \pm 147.5	244.7 \pm 146.8	-34.1 \pm 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

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

4 3.2. Motor assessment

5 Add-on CSAI significantly reduced motor fluctuations, as shown by the decrease in the
6 UPDRS-IV Fluctuations score (sum of Items 36-39), which improved by -1.04 ± 1.8 points (p
7 = 0.005). No other significant motor improvement was observed. In parallel, we observed a
8 trend towards an increase in the UPDRS-III ON medication score (non-dopaminergic
9 symptoms; $p = 0.09$) and the Schwab & England OFF medication score ($p = 0.09$), indicating
10 potential disease progression (Table 2).

11

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

	<i>N</i>	M0	M6	M6 - M0	<i>p</i> 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				
<i>Total score</i>		7.0 ± 3.3	5.8 ± 2.6	-1.2 ± 3.1	0.11
<i>Dyskinesia</i>		2.7 ± 2.4	2.3 ± 1.8	-0.4 ± 2.2	0.30
<i>Fluctuations</i>		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

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

4 3.3. Neuropsychological assessment

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

10

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

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

<i>Time (s)</i>		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

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2 *Note.* *SD* = standard deviation; TMT: Trail Making Test; MCST = Modified Wisconsin Card

3 Sorting Test; MDRS = Mattis Dementia Rating Scale; UPDRS-I = Unified Parkinson's

4 Disease Rating Scale Part I; MADRS = Montgomery and Åsberg Depression Rating Scale;

5 AMDPAT = AMDP-AT anxiety scale; AES = Apathy Evaluation Scale.

6 **3.4. Psychiatric assessment**

7 At 6 months follow up, no significant modification was observed in overall psychiatric

8 aspects (UPDRS-I), depression (MADRS), apathy (AES) or anxiety (AMDP-AT), despite

9 missing data for the three last scales, owing to the retrospective status of our study (Table 3).

10 Of the 22 patients, one patient developed impulse control disorders (sexual compulsion and

11 compulsive shopping) and another presented slight simple visual hallucinations. Both events

12 disappeared when the dopamine agonist treatment was reduced without any change in CSAI

13 treatment.

14 **3.5. Quality-of-life assessment**

15 The overall quality of life tended to improve, according to the total score of the SF-36 ($p =$

16 0.09). When we explored the subscores, we observed that the add-on CSAI treatment

17 improved physical domains, which were the most impaired at baseline, but also improved

18 psychological domains. The improvement in the physical composite subscore ($9.7\% \pm 13.9, p$

19 $= 0.01$) was sustained by a significant improvement in the bodily pain subscore ($13.9\% \pm$

20 $20.5, p = 0.02$) and a trend towards an improvement in the role physical subscore ($20.6\% \pm$

21 $40.7, p = 0.06$). In addition, we found a significant reduction in the bodily discomfort

22 subscore of the PDQ-39 ($9.2\% \pm 14.4, p = 0.01$). The psychological improvement was related

1 to both a significant decrease in the stigma subscore of the PDQ-39 ($10.9\% \pm 20.5$, $p = 0.01$)
 2 and a trend towards an improvement in the social functioning subscore of the SF-36 ($9.0\% \pm$
 3 23.4 , $p = 0.10$). Finally, at 6-month follow up, the mean CGI-I score was $66.4\% \pm 16.0$ (Table
 4 4).

5

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

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

8 *Note.* *SD* = standard deviation; SF-36 = 36-Item Short Form Survey; PDQ-39 = 39-item

9 Parkinson's Disease Questionnaire; CGI-I = Clinical Global Impression Improvement scale.

10 4 DISCUSSION

11

1 In the present study, we investigated for the first time the influence of 6 months of treatment
2 optimized with add-on CSAI on motor symptoms, cognitive and psychiatric domains, and
3 quality of life in 22 PD patients without cognitive impairment. The add-on CSAI was
4 associated with i) reduced motor fluctuations, ii) no change in cognition, iii) no change in
5 psychiatric domains, and iv) improved quality of life in physical and psychological aspects.
6 The overall results of the current study are in line with previous observations realized in more
7 advanced patients, indicating that add-on CSAI improves motor symptoms and quality of life
8 without altering cognition or inducing psychiatric symptoms [7–12,14,17].
9
10 The main result for motor function was a significant reduction in the motor fluctuation score,
11 confirming that add-on CSAI is efficient in this motor aspect [11,21]. This improvement
12 probably resulted from both the reduction in pulsatile levodopa treatments and the increase in
13 total LEDD through the introduction of the apomorphine infusion, although a specific role of
14 the apomorphine molecule cannot be ruled out.
15 As expected, cognitive functioning, as assessed with neuropsychological tools, was not
16 disturbed when we compared the same patients without cognitive deterioration at baseline and
17 6 months after the introduction of add-on CSAI. Our results confirm the absence of cognitive
18 change reported in previous observations for smaller samples with greater variations in
19 cognitive severity [7–11,13,14]. The only significant change that we found was a reduction in
20 the number of words correctly read during 45 seconds in the Stroop Word Test. This
21 reduction may suggest that add-on CSAI induces some degree of slowdown, as reported in
22 patients with a more severe disease [11]. However, unlike the study by Drapier et al. (2012),
23 this slowdown was not confirmed by other cognitive indices, such as colour naming accuracy
24 or the time taken to complete the TMT Part A, which actually tended to be shorter at 6 months
25 [11]. However, in another study using more sensitive tools to evaluate cognitive action control

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

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

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

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

7

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

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

4

5 **Conclusion**

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

13

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21

22 **Compliance with ethical standards**

23 **Conflicts of interest:** Dr Sophie Drapier received speech honorarium from Teva and

24 Medtronic and served on scientific advisory boards for Aguetant and Britannia. Pr Marc

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

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

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