



HAL
open science

Personality and quality-of-life improvement after apomorphine infusion in Parkinson's disease

Mathilde Boussac, Estelle Harroch, Christel Barthelemy, Fabienne Ory Magne, Clémence Leung, Margherita Fabbri, Christophe Arbus, Christine Brefel-Courbon

► To cite this version:

Mathilde Boussac, Estelle Harroch, Christel Barthelemy, Fabienne Ory Magne, Clémence Leung, et al.. Personality and quality-of-life improvement after apomorphine infusion in Parkinson's disease. Brain Communications, In press, 10.1093/braincomms/fcae181/7681913 . hal-04602369

HAL Id: hal-04602369

<https://hal.science/hal-04602369v1>

Submitted on 5 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Personality and quality-of-life improvement after apomorphine infusion in Parkinson's disease

Mathilde Boussac, PhD,^{1,*}, Estelle Harroch, MSc,², Christel Barthelemy, NP,², Fabienne Ory-Magne, MD,^{1,2}, Clémence Leung, MD,², Margherita Fabbri, MD, PhD,^{1,2}, Christophe Arbus, MD, PhD,^{1,3}, Christine Brefel-Courbon, MD, PhD,^{1,2}

Author affiliations:

1 Toulouse NeuroImaging Center, University of Toulouse, Toulouse, Inserm, UPS, France

2 Department of Clinical Pharmacology and Neurosciences, Parkinson Expert Center, Clinical Investigation Center, University Hospital of Toulouse, NeuroToul COEN (Center of Excellence in Neurodegeneration), Toulouse, NS-PARK/FCRIN Network, France

3 Psychiatry Department of the University Hospital of Toulouse, CHU Purpan, Toulouse, France

Correspondence to: Mathilde Boussac

Unité ToNIC, Toulouse NeuroImaging Center, UMR 1214 – INSERM/UPS – CHU PURPAN – Pavillon Baudot, Place du Dr Baylac, 31024 Toulouse, France

mathilde.boussac@inserm.fr.

Abstract

People with Parkinson's disease with motor fluctuations can be treated by Continuous Subcutaneous Apomorphine Infusion (CSAI) to reduce their symptoms. Nonetheless, factors are lacking to predict patients' quality-of-life amelioration after CSAI. This pilot study aimed to evaluate associations between personality dimensions and quality-of-life improvement after six months of CSAI.

Thirty-nine people with Parkinson's disease awaiting CSAI were included. Linear regression models between "Temperament and Character Inventory" personality dimensions at baseline

<https://mc.manuscriptcentral.com/braincom>

1
2
3 and percentage of change in PDQ-39 (Parkinson's Disease Questionnaire-39) scores after six
4 months of CSAI were realized (n=35). Temperament and Character Inventory was also
5 compared between patients awaiting CSAI and patients awaiting deep brain stimulation of the
6 sub-thalamic nucleus (n=39 from the PREDI-STIM study).
7
8
9

10 Higher Reward Dependence scores were associated with a better quality-of-life outcome after
11 six months of CSAI, while Self-Directedness scores were associated with a better quality of
12 life before CSAI (as opposed to Harm Avoidance, Reward Dependence, and Self-
13 Transcendence scores associated with a worse quality of life). Moreover, people with
14 Parkinson's disease awaiting deep brain stimulation of the sub-thalamic nucleus had similar
15 Temperament and Character Inventory dimensions compared to patients awaiting CSAI.
16
17
18
19
20

21 People with Parkinson's disease with higher Reward Dependence scores at baseline had the
22 best quality-of-life improvement after six months of CSAI. This finding could be used to better
23 prepare and accompany people with Parkinson's disease during CSAI establishment.
24 Moreover, this result could serve as an orientation factor to second-line treatments.
25
26
27
28
29
30

31 **Short title:** Personality and QoL improvement after CSAI
32
33
34

35 **Keywords:** Temperament and Character Inventory; Precision Medicine; Therapeutics
36
37
38
39

40 **Introduction**

41
42
43 Second-line treatments such as Deep Brain Stimulation of the Sub-Thalamic Nucleus (DBS-
44 STN) or Continuous Subcutaneous Apomorphine Infusion (CSAI) can be offered to people
45 with Parkinson's Disease (PwPD) with motor fluctuations¹. CSAI significantly reduces OFF
46 time in PwPD compared with placebo, but did not improve Quality of Life (QoL) in the double-
47 blind, randomized TOLEDO study², even if some open-label studies have found QoL
48 amelioration following CSAI³⁻⁷. Improvements in motor function, overall non-motor burden,
49 sleep, fatigue, mood, apathy and executive functions were also observed after 6 months of
50 CSAI in a recent prospective study⁸. Similarly, CSAI reduced motor fluctuations and improved
51 QoL without impacting cognition and psychiatric⁷. Finally, recent reviews confirmed all these
52 results: improvement in OFF-time duration and in various non-motor symptoms (including
53
54
55
56
57
58
59
60

1
2
3 neuropsychiatric disorders) following CSAI, as well as its safety and efficacy in people with
4 advanced PD^{9,10}.

5
6
7 Personality corresponds to each individual characteristic associated with behavior, cognition
8 and emotions in order to adapt to the environment¹¹, and it affects the perception of the impact
9 of illnesses on well-being and capabilities¹². Hence, personality was shown to be associated to
10 health-related QoL in different studies¹³, as previously reported in PD¹⁴. In this respect,
11 personality could be an interesting factor for predicting QoL improvement after CSAI, as it
12 was associated with QoL improvement after DBS-STN¹⁵ using the Temperament and Character
13 Inventory (TCI) (validated in a large cohort of PwPD¹⁶), which provides quantitative measure
14 of seven personality dimensions¹⁷.

15
16
17 In absence of randomized controlled trials comparing the improvement induced by second-line
18 treatments (DBS-STN vs CSAI)¹, patients' choice and clinical judgement remain the main
19 factors in treatment choice¹. Since our previous study showed that PwPD with higher Novelty
20 Seeking and Cooperativeness scores had the best improvement of QoL after DBS-STN¹⁵,
21 personality could help to select the best treatment.

22
23
24 This pilot study aimed to determinate associations between personality dimensions and QoL
25 improvement after six months of CSAI and as a secondary objective to evaluate associations
26 between personality dimensions and QoL before CSAI establishment. As complementary
27 objective, using additional data from our previous study, we aim to compare personality
28 dimensions between two cohorts of PwPD awaiting CSAI or DBS-STN.

29 30 31 32 33 34 35 36 37 38 39 40 41 42 **Materials and methods**

43 44 45 **Patients**

46
47
48 In this PSYCHO-PERF study, we included PwPD who started CSAI treatment from 2019 to
49 2022 in the University Hospital of Toulouse. CSAI introduction was decided in routine care
50 after medical evaluation.

51
52
53 PwPD presenting an atypical parkinsonian syndrome, a DBS device, a significant psychiatric
54 disorder, or cognitive decline (Montreal Cognitive Assessment (MoCA) score<24) were
55 excluded.
56
57
58
59
60

All patients gave their informed consent and PSYCHO-PERF study (clinicalTrials.gov n°NCT03793491) was approved by ethics committee (CPP Nord-Ouest IV).

As complementary objective, supplementary data from the PREDI-STIM cohort (Protocol 2013-A00193-42; clinicalTrials.gov n°NCT02360683) of the best-matched PwPD awaiting DBS-STN were extracted and used to compare PD patients awaiting CSAI or DBS-STN. Protocol can be found in our previous study¹⁴. Matching with PwPD awaiting CSAI was done according to age, disease duration and sex. When a “perfect match” was not available, we prioritized age and sex for matching, followed by only age, followed by only disease duration. Age and sex were chosen as matching criteria since both factors have been shown to influence TCI personality dimensions scores in different populations such as the normative French one¹⁸ and different psychiatric populations¹⁷. The supplementary table 1 presents the matched-characteristics of all the patients.

Methods

The primary objective of this pilot study was to evaluate associations between TCI personality dimensions and QoL improvement measured by the change in PDQ-39 scale after six months of CSAI. The secondary objectives were to determine associations between TCI personality dimensions and QoL before starting CSAI treatment and to compare personality dimensions of PwPD awaiting CSAI to those awaiting DBS-STN from the PREDI-STIM study¹⁴.

Motor and non-motor states (Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)¹⁹ in ON condition), depression (Hamilton Depression Rating Scale (HAM-D)²⁰), anxiety (Hamilton Anxiety Rating Scale (HAMA)²¹), apathy (Lille Apathy Rating Scale (LARS)²²) and QoL (Parkinson’s Disease Questionnaire-39 (PDQ-39)²³) were collected at baseline (V0) and six months after CSAI (V1). The PDQ-39, a self-questionnaire specific to PD, is divided into eight sub-scales of QoL with a mental component score (“Emotional Well-Being”, “Stigma”, “Social Support”, “Cognitions”, and “Communication”) and a physical component score (“Mobility”, “Activities of Daily Living” (ADL), and “Bodily Discomfort”), altogether forming a PDQ-39 Total score. A higher score indicates a worse QoL.

The TCI was used to assess patients’ personality across seven dimensions¹⁷ before CSAI (V0) and was not re-assessed after second-line treatment establishment, as in our previous study within the DBS-STN cohort¹⁵. This self-questionnaire of 226 items with binary responses

(true/false) is divided into four genetically determined temperaments (Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P)) and three characters, which are developed through growing (Self-Directedness (SD), Cooperativeness (C), and Self-Transcendence (ST)). Each dimension score represents a part of individual personality on a spectrum. The higher the score, higher the patient presents the associated personality dimension.

The daily total Levodopa Equivalent Dose (LED) was calculated for each patient according to levodopa treatments, dopaminergic agonists, COMT and MAO inhibitors and other antiparkinsonians²⁴, in accordance with the updated systematic review and proposals from Jost et al. (2023)²⁵.

Statistical analyses

As descriptive analyses, mean, standard deviation and range (min, max) were calculated for quantitative variables, and headcount and percentage for qualitative variables. Before the analyses, Shapiro tests were done to verify the variables' normality.

Concerning clinical, behavioral and motor evolution assessment after six months of CSAI, we compared the PDQ-39 Total score and eight sub-scores, the four parts of the MDS-UPDRS, the HAMD, the HAMA, the LARS and the LED between V0 and V1 using paired two-sample Mann-Whitney tests or paired two-sample t-tests.

Univariate linear regression models were used to evaluate associations between TCI dimensions (explicative variables) and i) PDQ-39 scores at V0 and ii) percentages of change in PDQ-39 at V1 (responses variables). Due to the small sample size and in order to avoid over-adjustment in the models, Pearson correlations were performed between each TCI dimension and each potentially relevant variable (age, disease duration, LED, MoCA, MDS-UPDRS, LARS, HAMA and HAMD). Only variables with significant correlations (p -value <0.05 and Pearson correlation coefficient ≥ 0.5) were then used as adjustment variables in the models.

Each PDQ-39 sub-scores and Total score at V0, and the percentages of change of each PDQ-39 sub-scores and Total score at V1 were separately used as response variables while scores of each TCI dimensions were used as explanatory variables, with previous significant correlated variables being used as adjustment. An FDR (False Discovery Rate) correction was applied for seven comparisons with calculation of q -values (FDR-adjusted p -values) for each model.

1
2
3 TCI dimensions and clinical parameters (age, disease duration, LED, PDQ-39, MDS-UPDRS,
4 LARS, HAMA and HAMD) were compared between PwPD with motor fluctuations awaiting
5 CSAI or DBS-STN using two-sample Mann-Whitney tests or two-sample t-tests.
6
7

8
9 All analyses were conducted on R Studio Software Version 2022.02.3 and a threshold of
10 bilateral statistical significance of 0.05 was used. FDR corrections were applied (q-values) and
11 interpretations were made carefully according to results strength.
12
13
14

15 16 17 **Results**

18
19
20 Forty PwPD with motor fluctuations awaiting CSAI were screened and thirty-nine were
21 included in the PSYCHO-PERF study (one patient refused the CSAI). At V1, we analyzed
22 thirty-five patients because of four drop-outs related to CSAI adverse effects (fatigue (n=1),
23 cutaneous intolerance (n=1), hallucinations (n=1), and nausea (n=1)). Demographic and
24 clinical parameters are presented in Table 1.
25
26
27

28
29 Due to COVID-19 pandemic and lockdown in France during part of the study (from March 17
30 to May 11, 2020), five PwPD were evaluated at V1 through phone calls. Nonetheless, this
31 unplanned evaluation did not seem to impact the result of our study since comparisons of data
32 at V1 between patients evaluated in the hospital center and by phone calls did not reveal any
33 significant difference.
34
35
36

37
38 At V1, significant reduction in oral LED, MDS-UPDRS-III-on, MDS-UPDRS-IV, PDQ-39 Total
39 scores, PDQ-39 “Emotional Well-being”, and “Stigma” sub-scores, HAMD and HAMA scores were
40 found. Only total LED (CSAI + oral medications) significantly increased (Table 1).
41
42
43

44 We only found significant Pearson correlation between Persistence dimension and disease
45 duration at V0 (Supplementary table 2). Therefore, disease duration was used as an adjustment
46 variable in the linear regression models using Persistence as explanatory variable.
47
48

49 Table 2 presents models with significant associations (FDR-corrected or not). At V0, after
50 FDR-correction, significant positive associations remained between Self-Transcendence and
51 PDQ-39 Total and “Communication” scores, between Reward Dependence and PDQ-39
52 “ADL” scores, and between Harm Avoidance and PDQ-39 “Emotional Well-being” scores.
53 Conversely, Self-Directedness and PDQ-39 “Emotional Well-being” scores were significantly
54 negatively associated (Table 2). At V1, after FDR-correction, only Reward Dependence tended
55 to be negatively associated with the percentage of change in PDQ-39 Total score (Table 2).
56
57
58
59
60

No significant difference in the TCI were found between PwPD awaiting DBS-STN compared to patients awaiting CSAI (Table 1), while significant clinical differences were found between both populations. Patients awaiting CSAI had lower LED, higher MDS-UPDRS II and III, PDQ-39 “Emotional Well-being”, HAMD and HAMA scores at baseline.

Discussion

Our study suggests that PwPD with higher Reward Dependence scores at baseline have a better QoL after six months of CSAI while Self-Directedness scores are associated with a better QoL before CSAI (as opposed to Harm Avoidance, Reward Dependence and Self-Transcendence scores associated with poorer QoL at baseline). Moreover, PwPD awaiting CSAI or DBS-STN had similar personality dimensions.

In accordance with the literature⁵, after six months of CSAI, our study confirmed a significant improvement of motor symptoms (MDS-UPDRS-III), motor complications (MDS-UPDRS-IV) and a significant decrease of daily oral LED²⁶. Global and mental/emotional parts of QoL were also significantly improved after CSAI, as in the literature^{3,4,6,26}, as well as anxiety-depressive state, again in line with the literature⁵.

Concerning our main objective, Reward Dependence was associated with QoL changes after CSAI: higher baseline Reward Dependence scores were associated with best QoL improvement. Reward Dependence corresponds to social and affective dependency with a need for social approval leading to sensible, loving and devoted individuals¹⁷. In this model of personality, Reward Dependence is related to the norepinephrine system¹⁷, as shown mainly by genetic studies^{27–29}. Although this model is questionable, there is no direct evidence that Reward Dependence can be linked to the dopaminergic system, making it difficult to establish a direct link with the role of apomorphine. In addition, apomorphine was also shown to interact with the norepinephrine system^{30,31}, hence an interaction between different neurotransmitters systems may certainly be involved in our results. Moreover, this personality dimension has already been associated with a better social part of QoL or a higher perception of social support in different patients populations^{32,33}. Therefore, due to its link with social dependence, PwPD with higher Reward Dependence before CSAI may have better social adaptation and are so less disrupted by wearing CSAI, allowing them to enjoy a better QoL after CSAI implementation. Conversely, some patients do not appreciate the CSAI because of its inconveniences / constraints²⁶ (pump wearing, daily infusion often carried out by a nurse or spouse, etc.) which

1
2
3 can lead to a negative feeling of lack / loss of independence and therefore a poor perception of
4 QoL. This dissatisfaction with the CSAI may result in the discontinuation of the pump³⁴ for
5 personal reasons²⁶, and poor compliance with the device³⁵. Moreover, a lack of patient support
6 (importance of “full-time caregivers”) has been related to CSAI discontinuation in some
7 cases³⁶, which may reveal the potential loss of independence associated with this treatment. As
8 a result, patients who are more socially adapted (higher Reward Dependence) may be less
9 affected by these disadvantages as they enjoy being cared for.

10
11
12 Furthermore, it is interesting to note that better QoL improvement after CSAI for patients with
13 high Reward Dependence was found for the overall QoL (PDQ-39 Total), rather than for the
14 social component usually found in the literature³².

15
16 Moreover, despite worst motor and anxio-depressive state in PwPD awaiting CSAI compared
17 to the ones awaiting DBS-STN, TCI personality dimensions were similar between both cohorts
18 of fluctuating PwPD awaiting second-line treatments. These demographical differences (LED,
19 motor and anxio-depressive state) may be explained by surgical selection criteria.

20
21 The main limitation of our study is the small sample size. Thus, to confirm the results of this
22 pilot study, we are currently conducting a multicentric study evaluating the relationships
23 between several bio-psycho-social factors (personality, believes about the treatment, ways of
24 copying, and social support) and the improvement in QoL after CSAI (ClinicalTrials.gov:
25 NCT06080399). Patient-Reported Outcome (PRO) measures are also another innovative and
26 important way of conducting research that we will consider in our future studies since it could
27 have a major impact in advanced therapies^{37,38}. Another limitation could be the absence of
28 behavioral variables (such as the anxio-depressive state) as adjustment in our models.
29 However, due to the small sample size, we only used relevant variables correlated with TCI
30 personality dimensions in order to avoid over-fitting in the models. In addition, we are aware
31 that a significant number of analyses was performed to evaluate the associations between the
32 seven personality dimensions and the QoL improvement after CSAI. Nevertheless, the use of
33 the FDR correction for each personality dimensions comparisons should validate the reliability
34 of our positive results. Our aim was to assess personality dimensions as predictors of improved
35 QoL and, therefore, they were only assessed prior to the implementation of the intervention.
36 Any personality changes induced by CSAI could be the subject of another study.

37
38
39 Finally, since we found different associations between personality and QoL outcome after
40 CSAI and DBS-STN¹⁵, personality dimensions could be used as a predictive factor of QoL
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 improvement to orientate patients toward their best second-line treatment. PwPD with higher
4 Reward Dependence scores could be preferably oriented towards CSAI, while PwPD with
5 higher Novelty Seeking and Cooperativeness scores could be preferably oriented towards DBS-
6 STN¹⁵. To implement this guideline in clinical practice, our team is currently validating a
7 decision algorithm based on personality to best guide PwPD towards DBS-STN.
8
9
10
11
12
13
14

15 **Data availability**

16
17 The data supporting the findings of this study are available on request from the corresponding
18 author.
19

20 **Acknowledgements**

21
22 We are thankful to all participants for their cooperation and to the promotor who enabled this
23 study (University Hospital of Toulouse).
24
25
26
27

28 **Funding**

29
30 Part of this research was funded by AXA Assurances VIE Mutuelle (France).
31
32

33 **Competing interests**

34
35 The authors report no competing interests.
36
37
38

39 **Supplementary material**

40
41 Supplementary material is available at *Brain Communications* online.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Clarke CE, Worth P, Grosset D, Stewart D. Systematic review of apomorphine infusion, levodopa infusion and deep brain stimulation in advanced Parkinson's disease. *Parkinsonism & Related Disorders*. 2009;15(10):728-741. doi:10.1016/j.parkreldis.2009.09.005
2. Katzenschlager R, Poewe W, Rascol O, et al. Long-term safety and efficacy of apomorphine infusion in Parkinson's disease patients with persistent motor fluctuations: Results of the open-label phase of the TOLEDO study. *Parkinsonism & Related Disorders*. 2021;83:79-85. doi:10.1016/j.parkreldis.2020.12.024
3. Dafsari HS, Martinez-Martin P, Rizos A, et al. EuroInf 2: Subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease. *Movement Disorders*. 2019;34(3):353-365. doi:10.1002/mds.27626
4. Drapier S, Eusebio A, Degos B, et al. Quality of life in Parkinson's disease improved by apomorphine pump: the OPTIPUMP cohort study. *J Neurol*. 2016;263(6):1111-1119. doi:10.1007/s00415-016-8106-3
5. Martinez-Martin P, Reddy P, Katzenschlager R, et al. EuroInf: A Multicenter Comparative Observational Study of Apomorphine and Levodopa Infusion in Parkinson's Disease. *Movement Disorders*. 2015;30(4):510-516. doi:10.1002/mds.26067
6. Martinez-Martin P, Reddy P, Antonini A, et al. Chronic Subcutaneous Infusion Therapy with Apomorphine in Advanced Parkinson's Disease Compared to Conventional Therapy: A Real Life Study of Non Motor Effect. *Journal of Parkinson's Disease*. 2011;1(2):197-203. doi:10.3233/JPD-2011-11037
7. Houvenaghel JF, Drapier S, Duprez J, et al. Effects of continuous subcutaneous apomorphine infusion in Parkinson's disease without cognitive impairment on motor, cognitive, psychiatric symptoms and quality of life. *J Neurol Sci*. 2018;395:113-118. doi:10.1016/j.jns.2018.10.010
8. Fernández-Pajarín G, Sesar Á, Jiménez Martín I, Ares B, Castro A. Continuous subcutaneous apomorphine infusion in the early phase of advanced Parkinson's disease: A prospective study of 22 patients. *Clin Park Relat Disord*. 2021;6:100129. doi:10.1016/j.prdoa.2021.100129
9. Gaire S, Kafle S, Bastakoti S, Paudel A, Karki K. Continuous Subcutaneous Apomorphine Infusion in Advanced Parkinson's Disease: A Systematic Review. *Cureus*. 2021;13(9):e17949. doi:10.7759/cureus.17949
10. Kukkle PL, Garg D, Merello M. Continuous Subcutaneous Infusion Delivery of Apomorphine in Parkinson's Disease: A Systematic Review. *Mov Disord Clin Pract*. 2023;10(9):1253-1267. doi:10.1002/mdc3.13810
11. Markett S, Montag C, Reuter M. Anxiety and Harm Avoidance. In: *Neuroimaging Personality, Social Cognition, and Character*. Elsevier; 2016:91-112. doi:10.1016/B978-0-12-800935-2.00005-1

12. Lahey BB. Public health significance of neuroticism. *American Psychologist*. 2009;64(4):241-256. doi:10.1037/a0015309
13. Huang IC, Lee JL, Ketheeswaran P, Jones CM, Revicki DA, Wu AW. Does personality affect health-related quality of life? A systematic review. *PLoS One*. 2017;12(3):e0173806. doi:10.1371/journal.pone.0173806
14. Boussac M, Arbus C, Dupouy J, et al. Personality Dimensions Are Associated with Quality of Life in Fluctuating Parkinson's Disease Patients (PSYCHO-STIM). *Journal of Parkinson's Disease*. 2020;10(3):1057-1066. doi:10.3233/JPD-191903
15. Boussac M, Arbus C, Klinger H, et al. Personality Related to Quality-of-Life Improvement After Deep Brain Stimulation in Parkinson's Disease (PSYCHO-STIM II). *Journal of Parkinson's Disease*. 2022;12(2):699-711. doi:10.3233/JPD-212883
16. Boussac M, Arbus C, Colin O, et al. Personality assessment with Temperament and Character Inventory in Parkinson's disease. *Parkinsonism & Related Disorders*. 2022;103:34-41. doi:10.1016/j.parkreldis.2022.08.004
17. Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. *The Temperament and Character Inventory (TCI): A Guide to Its Development and Use*. Center for Psychobiology of Personality, Washington University; 1994.
18. Pélioso A, Lépine JP. Normative data and factor structure of the Temperament and Character Inventory (TCI) in the French version. *Psychiatry Res*. 2000;94(1):67-76. doi:10.1016/s0165-1781(00)00127-x
19. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. 2008;23(15):2129-2170. doi:10.1002/mds.22340
20. Hamilton M. A Rating Scale for Depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 1960;23(1):56-62. doi:10.1136/jnnp.23.1.56
21. Hamilton M. The Assessment of Anxiety States by Rating. *British Journal of Medical Psychology*. 1959;32(1):50-55. doi:https://doi.org/10.1111/j.2044-8341.1959.tb00467.x
22. Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2006;77(5):579-584. doi:10.1136/jnnp.2005.075929
23. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res*. 1995;4(3):241-248. doi:10.1007/BF02260863
24. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders*. 2010;25(15):2649-2653.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
25. Jost S, Kaldenbach MA, Antonini A, et al. Levodopa Dose Equivalency in Parkinson's Disease: Updated Systematic Review and Proposals. *Movement Disorders*. Published online May 5, 2023. doi:10.1002/mds.29410
 26. Meira B, Degos B, Corsetti E, et al. Long-term effect of apomorphine infusion in advanced Parkinson's disease: a real-life study. *npj Parkinsons Dis*. 2021;7(1):1-11. doi:10.1038/s41531-021-00194-7
 27. Curtin F, Walker JP, Peyrin L, Soulier V, Badan M, Schulz P. Reward dependence is positively related to urinary monoamines in normal men. *Biol Psychiatry*. 1997;42(4):275-281. doi:10.1016/S0006-3223(96)00364-2
 28. Garvey MJ, Noyes R, Cook B, Blum N. Preliminary confirmation of the proposed link between reward-dependence traits and norepinephrine. *Psychiatry Res*. 1996;65(1):61-64.
 29. Ham BJ, Choi MJ, Lee HJ, Kang RH, Lee MS. Reward dependence is related to norepinephrine transporter T-182C gene polymorphism in a Korean population. *Psychiatr Genet*. 2005;15(2):145-147.
 30. Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A. Differential Actions of Antiparkinson Agents at Multiple Classes of Monoaminergic Receptor. I. A Multivariate Analysis of the Binding Profiles of 14 Drugs at 21 Native and Cloned Human Receptor Subtypes. *J Pharmacol Exp Ther*. 2002;303(2):791-804. doi:10.1124/jpet.102.039867
 31. Ribarič S. The Pharmacological Properties and Therapeutic Use of Apomorphine. *Molecules*. 2012;17(5):5289-5309. doi:10.3390/molecules17055289
 32. Masthoff ED, Trompenaars FJ, Van Heck GL, Hodiament PP, De Vries J. The relationship between dimensional personality models and quality of life in psychiatric outpatients. *Psychiatry Research*. 2007;149:1-3.
 33. Demirci K, Demirci S, Taşkıran E, Kutluhan S. The effects of temperament and character traits on perceived social support and quality of life in patients with epilepsy. *Epilepsy & Behavior*. 2017;74:22-26. doi:10.1016/j.yebeh.2017.05.039
 34. Henriksen T, Staines H. Continuous Subcutaneous Apomorphine Infusion in Parkinson's Disease: A Single-Center, Long-Term Follow-Up Study of the Causes for Discontinuation. *Journal of Personalized Medicine*. 2021;11(6):525. doi:10.3390/jpm11060525
 35. Olivola E, Fasano A, Varanese S, et al. Continuous subcutaneous apomorphine infusion in Parkinson's disease: causes of discontinuation and subsequent treatment strategies. *Neurol Sci*. 2019;40(9):1917-1923. doi:10.1007/s10072-019-03920-5
 36. Phokaewvarangkul O, Anan C, Phimpha A, Chaudhuri KR, van Laar T, Bhidayasiri R. Early factors for predicting discontinuation to subcutaneous Apomorphine infusion in Parkinson's disease: A prospective analysis of the Thai Apomorphine Registry. *Parkinsonism & Related Disorders*. 2021;91:146-151. doi:10.1016/j.parkreldis.2021.09.022
 37. Reddy P, Martinez-Martin P, Brown RG, et al. Perceptions of symptoms and expectations of advanced therapy for Parkinson's disease: preliminary report of a Patient-Reported

1
2
3 Outcome tool for Advanced Parkinson's disease (PRO-APD). *Health and Quality of Life*
4 *Outcomes*. 2014;12(1):11. doi:10.1186/1477-7525-12-11
5

- 6
7 38. Martinez-Martin P, Rodriguez-Blazquez C, Frades-Payo B. Specific patient-reported
8 outcome measures for Parkinson's disease: analysis and applications. *Expert Review of*
9 *Pharmacoeconomics & Outcomes Research*. 2008;8(4):401-418.
10 doi:10.1586/14737167.8.4.401
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ACCEPTED MANUSCRIPT

TABLES

Table 1. Characteristics of PwPD awaiting CSAI or DBS-STN

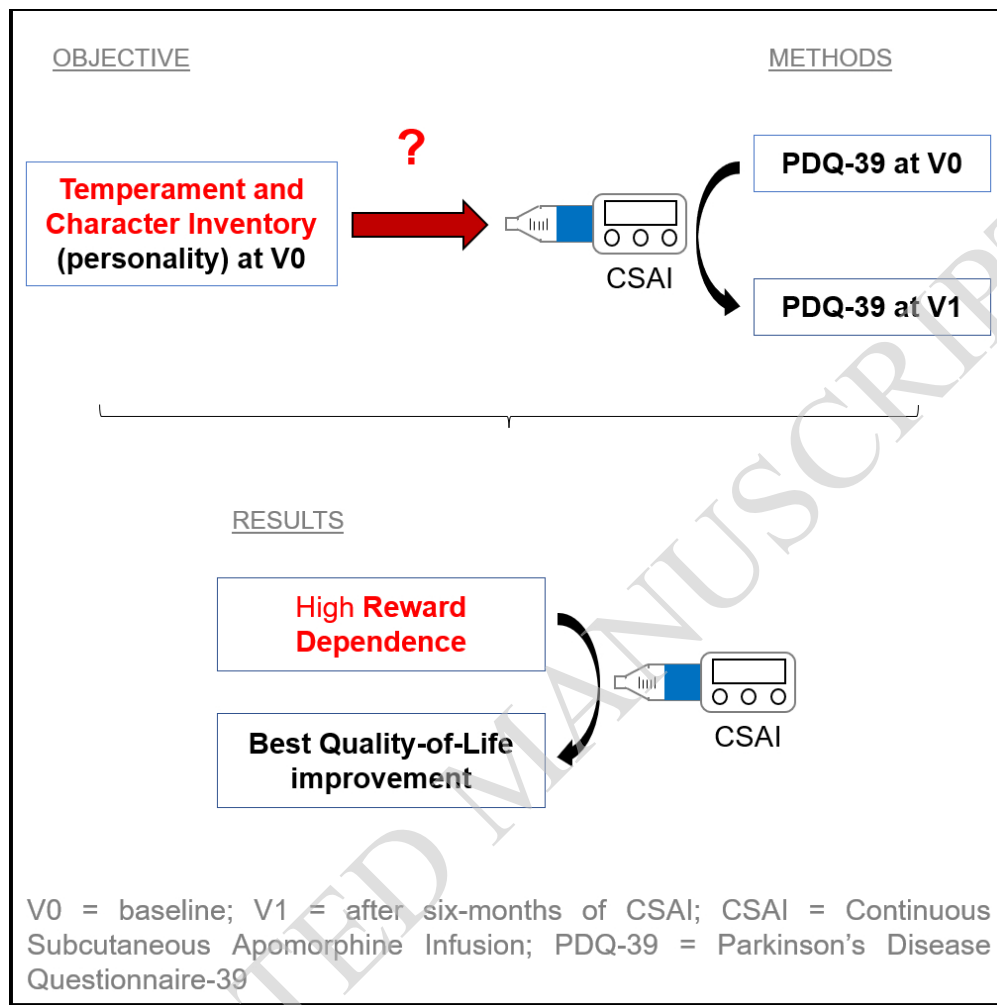
| Variables | CSAI-PD patients | | V0 vs V1 – p-value [95% CI of the difference] ¹ | DBS-STN-PD patients V0 (n=39) | CSAI vs DBS- STN – p-value [95% CI of the difference] ² |
|--------------------------|------------------------|------------------------|--|-------------------------------------|---|
| | V0 (n=39) | V1 (n=35) | | | |
| Sex F/M (N (%)) | 17 (44%) / 22 (56%) | 15 (43%) / 20 (57%) | / | 16 (41%) / 23 (59%) | / |
| Age (years) | 66.4 ± 6.4 | / | / | 65.1 ± 5.3 | 0.25 [-1.4; 1.4] |
| Disease duration (years) | 10.7 ± 3.7 | / | / | 10.5 ± 3.5 | 0.83 [-1.4; 1.8] |
| Total LED (mg/day) | 1008.9 ± 401.4 | 1452.1 ± 449 | 8e-7 [-569.5; -287.3] | 1318.7 ± 436.4 | 0.002 [-495.5; 113.3] |
| Pump LED (mg/day) | / | 716.6 ± 178.9 | / | / | / |
| Oral LED (mg/day) | 1008.9 ± 401.4 | 735.5 ± 354.2 | 8e-6 [186.6; 390.8] | / | / |
| MDS-UPDRS-I | 11.8 ± 5 | 12.5 ± 5.7 | 0.23 [-3; 0.5] | 10.3 ± 5.4 | 0.26 [-1.3; 0.3] |
| MDS-UPDRS-II ON | 14.2 ± 5.9 | 14.6 ± 6 | 0.54 [-2.2; 1.2] | 7.3 ± 6.4 | 1e-5 [5; 10] |
| MDS-UPDRS-III ON | 23.7 ± 12.1 | 16.2 ± 12.9 | 0.008 [2.5; 11.5] | 15.9 ± 9.1 | 0.004 [2.6; 12.9] |
| MDS-UPDRS-IV | 9.3 ± 2.5 | 6.4 ± 3.4 | 0.002 [1; 3.8] | 9.5 ± 3.5 | 0.73 [-1.7; 1.2] |
| CGI-S | / | 2.3 ± 0.7 | / | / | / |
| PDQ-39 Total | 33.1 ± 12.2 | 27.4 ± 10.3 | 0.005 [1.7; 8.4] | 30.1 ± 12.4 | 0.29 [-2.6; 3.5] |
| Mobility | 38.7 ± 21.3 | 33.8 ± 21.3 | 0.18 [-2.1; 10.7] | 36.6 ± 20.1 | 0.66 [-7.3; 11.4] |
| ADL | 35.6 ± 18.3 | 33.2 ± 16.7 | 0.14 [-1.2; 8.1] | 38.5 ± 19.8 | 0.51 [-11.5; 5.7] |
| Emotional well-being | 41.5 ± 20.6 | 30.8 ± 20 | 0.004 [4.2; 16.7] | 29.9 ± 15.7 | 0.007 [3.3; 9.8] |
| Stigma | 31.3 ± 19 | 19.3 ± 17.6 | 0.001 [6.3; 18.8] | 32.5 ± 25.5 | 0.88 [-12.5; 12.5] |
| Social support | 12.5 ± 13.6 | 8.1 ± 13.6 | 0.22 [-4.2; 16.7] | 8.8 ± 15 | 0.07 [0; 3.3] |
| Cognition | 31.9 ± 17.3 | 28.8 ± 16.3 | 0.46 [-3.1; 6.7] | 26 ± 16.6 | 0.13 [-1.7; 13.6] |
| Communication | 28.6 ± 21.4 | 24.8 ± 18.7 | 0.47 [-4.2; 16.7] | 25 ± 19.4 | 0.42 [-8.3; 16.7] |
| Bodily Discomfort | 44.7 ± 20.9 | 40.2 ± 22.6 | 0.23 [-3.2; 12.7] | 43.8 ± 20.5 | 0.62 [-8.3; 16.7] |
| LARS | -27.2 ± 4.3 | -27.8 ± 4.1 | 0.25 [-1; 2.5] | -27 ± 4.6 | 0.88 [-2.2; 1.9] |
| HAMD | 8.8 ± 4.6 | 6.6 ± 4 | 0.006 [0.6; 3.2] | 4.8 ± 4.2 | 4e-5 [3; 6] |
| HAMA | 10.2 ± 4.9 | 8.6 ± 4.8 | 0.03 [0; 2.5] | 4.9 ± 5.1 | 3e-6 [4; 7] |
| TCI dimensions | | | | | |
| Novelty Seeking (NS) | 17.3 ± 5 | / | / | 15.5 ± 4.4 | 0.09 [-0.3; 3.9] |
| Harm Avoidance (HA) | 18.8 ± 6.4 | / | / | 17.6 ± 6.1 | 0.42 [-1.7; 1.4] |
| Reward Dependence (RD) | 15.4 ± 3.2 | / | / | 14.5 ± 3.9 | 0.25 [-0.7; 2.5] |
| Persistence (P) | 5.4 ± 1.6 | / | / | 5.5 ± 1.7 | 0.84 [-1.1; 1.1] |
| Self-Directedness (SD) | 31.7 ± 6.4 | / | / | 34 ± 5.8 | 0.10 [-5.1; 9.4] |
| Cooperativeness (C) | 32.5 ± 5.1 | / | / | 33.4 ± 4.6 | 0.18 [-3; 1.1] |
| Self-Transcendence (ST) | 14.2 ± 5.7 | / | / | 14.9 ± 6.7 | 0.70 [-4; 1.3] |

Mean ± SD; ¹ paired two-sample Mann-Whitney tests or t-tests between V0 and V1; ² two-sample Mann-Whitney tests or t-tests between PwPD awaiting CSAI or DBS-STN; significant p-values in bold; PD = Parkinson's Disease; CSAI = Continuous Subcutaneous Apomorphine Infusion; DBS-STN = Deep Brain Stimulation of the Sub-Thalamic Nucleus; CI = Confidence Interval; F/M = Female/Male; LED = Levodopa Equivalent Dosage; MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale; ON = medication state; ADL = Activities of Daily Living; LARS = Lille Apathy Rating Scale; HAMD=Hamilton Depression scale; HAMA=Hamilton Anxiety scale; TCI = Temperament and Character Inventory

Table 2. Significant associations between TCI dimensions at V0 and PDQ-39 scores at V0 (n=39) and percentages of change in PDQ-39 at V1 (n=35)

| PDQ-39 scale and sub-scales | TCI dimensions | Coefficients | p-value | q-value | R ² | |
|-----------------------------|----------------------|--------------|---------|---------|----------------|--------------|
| PDQ-39 at V0 | Total | SD | -0.63 | 0.04 | 0.13 | 0.09 |
| | | ST | 0.98 | 0.003 | 0.02 | 0.19 |
| | Mobility | ST | 1.35 | 0.02 | 0.17 | 0.11 |
| | | ADL | RD | 2.87 | 0.001 | 0.009 |
| | Emotional well-being | HA | 1.58 | 0.002 | 0.007 | 0.22 |
| | | SD | -1.54 | 0.002 | 0.007 | 0.21 |
| | Stigma | HA | 1.12 | 0.02 | 0.06 | 0.12 |
| | | SD | -1.11 | 0.02 | 0.06 | 0.12 |
| | Social support | C | -0.93 | 0.03 | 0.20 | 0.10 |
| | | SD | -0.91 | 0.04 | 0.08 | 0.09 |
| | Cognition | C | -1.22 | 0.02 | 0.08 | 0.11 |
| | | ST | 1.26 | 0.01 | 0.06 | 0.15 |
| | Communication | RD | 2.31 | 0.03 | 0.11 | 0.09 |
| | | ST | 1.62 | 0.006 | 0.04 | 0.16 |
| | Bodily Discomfort | C | 1.57 | 0.02 | 0.11 | 0.13 |
| Changes in PDQ-39 (%) at V1 | Total | RD | -4.73 | 0.008 | 0.05 | 0.17 |
| | ADL | P | -12.71 | 0.03 | 0.20 | 0.09 |

Significant q-values (FDR-corrected p-value) in bold; ADL = Activities of Daily Living; SD = Self-Directedness; ST = Self-Transcendence; RD = Reward Dependence; HA = Harm Avoidance; C = Cooperativeness; P = Persistence



Graphical abstract

434x436mm (59 x 59 DPI)