Journal of Parkinson's Disease 14 (2024) 209–219
DOI 10.3233/JPD-230201
IOS Press

Research Report

Terminal Care in Parkinson's Disease: Real-Life Use of Continuous Subcutaneous Apomorphine Infusion to Improve Patient Comfort

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Accepted 26 November 2023
Pre-press 4 January 2024
Published 23 January 2024

Abstract.
Background: There are currently no recommendations on the therapeutic management of Parkinson's disease (PD) patients at the end of life.
Objective: To describe a cohort of patients with PD who benefited from continuous subcutaneous apomorphine infusion (CSAI) initiation at the end of their life as comfort care.
Methods: This real-life cohort includes 14 PD patients, who benefited from 24-h, low-dose CSAI (0.5–3 mg/h) in the context of terminal care. Patient's comfort (pain, rigidity, and/or ability to communicate) and occurrence of CSAI-related side-effects (nausea/vomiting, cutaneous and behavioral manifestations) were evaluated based on medical records.

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Results: All patients (age 62–94 years, disease duration 2–32 years) presented with late-stage PD and a compromised oral route. Treatment lasted from a few hours to 39 days. CSAI led to substantial functional improvement, with a good safety profile. Overall clinical comfort was deemed improved by the medical team, the patient, and/or caregivers.
Conclusions: CSAI might be a promising approach in PD terminal care, as it reduces motor symptoms and overall discomfort, with an apparent good safety profile. Use of the apomorphine pen, sublingual film or a classic syringe pump might be considered when apomorphine pumps are not available. Larger observational cohorts and randomized controlled trials are needed to establish the efficacy and tolerability of apomorphine in the context of terminal care and more broadly, in an advance care planning perspective.

Keywords: Neuropalliative care, continuous subcutaneous apomorphine infusion (CSAI), dopaminergic withdrawal, symptoms relief, terminal care, Parkinson's disease, interdisciplinary care, patients' comfort

INTRODUCTION

Palliative care (PC) is a growing field of interest in neurology, particularly in late-stage Parkinson's disease (LSPD) [1–3]. Beyond motor symptoms, LSPD patients exhibit a variety of nonmotor symptoms (fatigue, pain, and neuropsychiatric disorders) that greatly affect their quality of life and that of their relatives, especially at the end of their life [1, 4]. Progressive or sudden swallowing difficulties are common in the terminal stage, leading to a compromised oral route and subsequent dopaminergic deprivation [5, 6]. Complications such as withdrawal syndromes and aspiration pneumonia may arise, further exacerbating clinical decline, and precipitating death in some cases [5–8]. Compensating for an inaccessible oral route therefore seems critical at this stage [4, 8]. Alternative routes of administration, such as rotigotine patch, have been explored, but not without significant side effects requiring ethical considerations [4, 5, 9–11]. One case report pointed to the benefit of apomorphine as a subcutaneous injection in the context of comfort care [10]. Here, we describe the initiation of *continuous* subcutaneous apomorphine *infusion* (CSAI) for symptoms relief and terminal care.

METHODS

In this retrospective case series, clinical data from 14 deceased PD patients who benefited from CSAI as terminal care were collected. Ethics committee approval was granted by Comité Est II.

In this cohort, the classic palliative medications used in France, namely scopolamine, opiates, and benzodiazepines, were unsuccessful in relieving signs of PD-related discomfort. This, associated with persistent swallowing disorders, prompted the initiation of CSAI as comfort care, either as an outpatient (home, nursing home) or inpatient setting. Demographic data, PD characteristics, trajectory of decline, predictors of end-of-life, clinical condition after CSAI initiation, side effects, and medications use were analyzed. Patient comfort was assessed based on medical files, evaluations by neurologists, PC physicians, PD nurses, and caregivers' reports when available.

RESULTS

Patients characteristics are described in Tables 1–4, according to their trajectory of decline (acute: Tables 1 and 2; slow: Tables 3 and 4) and place of death (home: Tables 1 and 3; hospital: Tables 2 and 4). On average, patients were 79 years old (62–94) with a mean PD duration of 15,3 years (2–32). All were LSPD patients presenting end-of-life predictors [12] and swallowing disorders, as evidenced by erratic adherence ($N = 5$) or nil-by-mouth condition ($N = 9$). Two patients already benefited from a device-aided therapy, excluding apomorphine pump. Most patients ($N = 9$) were apomorphine naïve.

Following days or weeks-long erratic adherence, progressive tapering, or sudden discontinuation of antiparkinsonian medications, all patients exhibited severe resurgence of PD symptoms. In some cases, symptoms were suggestive of the onset of malignant syndrome due to levodopa withdrawal (rigidity, reduced alertness, dysautonomia, dysphagia, autonomic impairment) [8]. In all cases, dopaminergic deprivation led to functional limitations (including impaired communication, pain and/or severe rigidity) with marked decline that prompted neuropalliative assessments.

Outpatient [13] or inpatient CSAI initiation was provided under the supervision of a neurologist and/or a PC physician (see Tables 1–4). A PD nurse (either from the hospital or home care services) was

Table 1
Characteristics and terminal care management of patients with late-stage Parkinson's disease and an *acute* trajectory of decline who died at home

		Case 1	Case 2
Patients' demographics	Age (y)	75	81
	Sex	M	F
Parkinson's disease characteristics and treatment	Disease duration (y)	8	Unknown
	Hoehn & Yahr stage	5	5
	Levodopa Equivalent Daily Dose (mg)	670	450
	Current use of LCIG	No	No
	Current use of DBS	No	No
	Current use of CSAI	No	No
	Apomorphine naïve	Yes	Yes
	Clozapine (chronic use)	No	No
End-of-life characteristics	Trajectory of decline	Acute (following a benign skin resection surgery)	Acute
	End-of-life predictors (according to Akbar et al. [12])	• Weight loss • decline in body condition • worsening of motor signs • cognitive decline	• Decline in body condition • hyperthermia suggestive of NLMS
	Relevant comorbidities (cancer, organ failure)	N/A	N/A
	Withdrawal from oral dopaminergic medications	Yes/documented/21 days	Yes/documented/4 days
	Nil by mouth (at the time of evaluation)	Yes	Yes
CSAI as terminal care	Decision to initiate CSAI	Neurologist	Neurologist
	Place of CSAI initiation	Home (following patient's request)	Nursing home
	Clinical condition before CSAI initiation	• Patient bedridden and in pain • Marked axial and segmental rigidity • Patient no longer able to communicate or to take his medications	• Severe swallowing disorders • Dystonia • Pain • Amimia
	Apomorphine dose (initial and final)	Titration up to 3 mg/h during the day 1 mg/h at night: total 36 mg/day	1 mg/h up to 2 mg/h over 24 h
	Clinical condition after CSAI initiation	• Improvement in rigidity • patient able to communicate with his relatives	• Less painful mobilizations during comfort care • Dystonia reduction • General soothing effect
	CSAI duration	10 days	7 days
	CSAI side effects	None reported	Increased sleepiness
	CSAI-induced clozapine initiation	Yes (Clozapine 25 mg: 0.5 tablet/day)	No
	CSAI-induced domperidone initiation	No	No
Terminal management	Palliative sedation	No	No
	Scopolamine	No	No
	Opiates	No	Transdermal fentanyl
	Benzodiazepines	No	Midazolam IV
	Others	N/A	N/A
	Place of death	Home (following patient's request)	Nursing home

LCIG, Levodopa-carbidopa intestinal gel; DBS, deep brain stimulation; CSAI, continuous subcutaneous apomorphine infusion; PD, Parkinson's disease; PC, palliative care; LTCF, long term care facility. *Palliative sedation or continuous deep sedation until death as defined by French Act n° 2016-87 of February 2, 2016, known as the Clayes Leonetti law.

Table 2
Characteristics and terminal care management of patients with late-stage Parkinson's disease and an *acute* trajectory of decline who died at the hospital

		Case 3	Case 4	Case 5	Case 6	Case 7
Patients' demographics	Age (y)	77	77	81	80	62
	Sex	F	F	F	F	F
Parkinson's disease characteristics and treatment	Disease duration (y)	32	12	8	9	2
	Hoehn & Yahr stage	5	5	4	4	5
	Levodopa Equivalent Daily Dose (mg)	700	1680	600	400	310
	Current use of LCIG	No	Yes	No	No	No
	Current use of DBS	Yes	No	No	No	No
	Current use of CSAI	No	No	No	No	No
	Apomorphine naïve	Yes	No (2016–2019, previous history of behavioral side effects: hallucinations, psychosis)	Yes	Yes	Yes
	Clozapine (chronic use)	Yes (stopped 5 days before death)	Yes (stopped 48 h before death)	No	Yes, stopped 48 h before death.	No
End-of-life characteristics	Trajectory of decline	Acute (neurostimulator infection)	Acute (acute pancreatitis+stroke)	Acute (aspiration pneumonia)	Acute (sepsis, abdominal pain)	Acute (cancer)
	End-of-life predictors (according to Akbar et al. [12])	• Onset of swallowing disorders • cognitive decline	• Worsening of axial motor signs • increased frequency of falls due to postural instability and dysautonomia • cognitive decline	• Dramatic loss of body weight • recurrent aspiration pneumonia	• Worsening of axial motor signs • increased frequency of falls due to postural instability and dysautonomia • cognitive decline	• Decline in body condition • weight loss • swallowing disorders • worsening of motor condition
	Relevant comorbidities (cancer, organ failure)	N/A	N/A	Peritoneal carcinomatosis	Colorectal cancer with liver metastases	Small cell carcinoma with multi-metastatic spread
	Withdrawal from oral dopaminergic medications	Yes/documented/7 days	Yes (gastrointestinal issues)/unknown duration	No, but erratic adherence	No, but erratic adherence	Yes/documented/a few days
	Nil by mouth (at the time of evaluation)	No	Yes	Yes	No	Yes

CSAI as terminal care	Decision to initiate CSAI	Neurologist+PC specialist	Neurologist	Neurologist	Neurologist	Neurologist+PC specialist
	Place of CSAI initiation	PC unit	PC Unit	PC Unit	PC Unit	PC Unit
	Clinical condition before CSAI initiation	• Patient bedridden • Marked axial and segmental rigidity • Patient unable to walk and communicate	• Segmental rigidity • Pain with even the smallest movement • Pressure sores and sore on right ear • Triple flexion	• Patient bedridden • In pain • Unable to communicate	• Onset of segmental rigidity • Painful movement	• Important akineto-rigid syndrome • Amimia • Diffuse pain (mobilizations) • Constipation
	Apomorphine dose (initial and final)	Titration up to 2 mg/h over 24 h	0.5 mg/h over 24 h	Titration up to 1 mg/h over 24 h	1 mg/h over 24 h	1 mg/h up to 2 mg/h over 24 h, 2 mg bolus as needed
	Clinical condition after CSAI initiation	• Improvement in rigidity • Pain relief	• Decreased stiffness in upper limbs • Less whimpers during nursing care	• Pain relief • Decreased rigidity during nursing care	• Pain relief • Improvement in rigidity	• Disappearance of the akineto-rigid syndrome and pain • Decrease in amimia • Normalization of transit • Improvement of communication abilities
	CSAI duration	5 days	Less than 24 h	9 days	1 day	10 days
	CSAI side effects	None reported	None reported	None reported	None reported	None reported
	CSAI-induced clozapine initiation	No (previous use)	No (previous use)	No	No (previous use)	No
	CSAI-induced domperidone initiation	No	No	No	No	No
Terminal management	Palliative sedation	No	No	No	No	No
	Scopolamine	No	No	No	No	Yes (single administration of 20 mg)
	Opiates	Morphine up to 24 mg/day 4 mg bolus on demand	Morphine 20 mg/day via IV increased a few hours before death to 40 mg/day	Morphine up to 24 mg/day 6 mg bolus on demand	Slow-release Oxycodone 60 mg/day and interdose of 10 mg if needed Switch to IV morphine 30 mg/day+3 mg boli, 24 h before death	Morphine IV: 12 mg/day then 19 mg/day then lowered to 14 mg/day the last 24 h Bolus of 2 mg
	Benzodiazepines	No	Diazepam 5 mg (before care)	No	Oxazepam 10 mg x 3/day at admission switch to IV Diazepam 5 mg twice a day, 24 h before death	Midazolam IV: 0.5 mg/h; lowered to 0.3 mg/hr secondarily, 0.5 mg bolus
	Others	N/A	N/A	N/A	N/A	N/A
	Place of death	PC unit	PC Unit	PC Unit	PC Unit	PC Unit

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Table 3
Characteristics and terminal care management of patients with late-stage Parkinson's disease and a *slow* trajectory of decline who died at home.

		Case 8	Case 9	Case 10	Case 11	Case 12
Patients' demographics	Age (y)	84	82	80	94	88
	Sex	M	F	F	F	M
Parkinson's disease characteristics and treatment	Disease duration (y)	8	Unknown	Unknown	25	20
	Hoehn & Yahr stage	5	5	5	5	5
	Levodopa Equivalent Daily Dose (mg)	500	300 mg	400	Unknown	230
	Current use of LCIG	No	No	No	No	No
	Current use of DBS	No	No	No	No	No
	Current use of CSAI	No	No	No	No	No
	Apomorphine naïve	Yes	No	No	No	Yes
	Clozapine (chronic use)	No	No	No	No	No
End-of-life characteristics	Trajectory of decline	Late-stage PD (difficulty swallowing, cessation of oral treatments)	Late-stage PD	Late-stage PD	Late-stage PD	Late-stage PD
	End-of-life predictors (according to Akbar et al. [12])	• Motor deterioration, became bedridden • dysautonomia	• Decline in body condition • swallowing disorders • falls	• Decline in body condition • swallowing disorders	• Decline in body condition • swallowing disorders	• Decline in body condition • swallowing disorders • worsening of motor condition
	Relevant comorbidities (cancer, organ failure)	N/A	N/A	N/A	N/A	N/A
	Withdrawal from oral dopaminergic medications	Yes/documented/3 days	Yes/documented/3 weeks	Erratic adherence	Erratic adherence	Erratic adherence
	Nil by mouth (at the time of evaluation)	No	Yes	No	No	Yes

CSAI as terminal care	Decision to initiate CSAI	Neurologist+PC specialist	Neurologist+PC specialist	PC specialist	Neurologist	Neurologist+General practitioner
	Place of CSAI initiation	Geriatric Unit	Nursing home	Nursing home	Home	Home
	Clinical condition before CSAI initiation	• Patient bedridden • Patient seized up with general stiffness • Unable to communicate or eat/be fed	• Severe swallowing disorders • Painful dystonia • Pain • Amimia	• Hypertonia • Pain • Swallowing disorders	• Swallowing disorders • Pain	• Severe cognitive decline • Altered motor status (increased retropulsion, stiffness, severe morning dystonia) • Patient unable to swallow nor communicate
	Apomorphine dose (initial and final)	0.5 mg/h over 24 h, then 1.5 mg/h over 24 h	1 mg/h up to 2 mg/h over 24 h	1 mg/h up to 2 mg/h over 24 h	1 mg/h (7am to 7pm) up to 3 mg/h over 24h	1 mg/h over 24 h
	Clinical condition after CSAI initiation	• Pain relief • Patient able to speak • Improved swallowing • Less clear effectiveness regarding stiffness	• Reduction of dystonia • Improved communication • Improved participation in care, transfer to chair possible	• Reduction of hypertonia during nursing care • Pain relief (hetero-evaluation by the care team)	Pain and stiffness requiring increased pump flow rates	• Significant reduction in suffering signs • Improvement in lower limbs stiffness • Decrease in nocturnal agitation
	CSAI duration	21 days	21 days	25 days	39 days	19 days
	CSAI side effects	None reported	Increased sleepiness	None reported	None reported	None reported
	CSAI-induced clozapine initiation	No	No	No	No	No
	CSAI-induced domperidone initiation	Yes	No	No	No	No
Terminal management	Palliative sedation	No	No	No	No	No
	Scopolamine	No	No	No	No	No
	Opiates	No	Morphine (following the fall, 48 h prior to the death)	Morphine	Morphine 12 mg/day	No
	Benzodiazepines	No	Midazolam IV (following the fall, 48 h prior to the death)	Midazolam	Midazolam 2 mg/h	No
	Others	N/A	N/A	N/A	N/A	N/A
	Place of death	Home (following patient's request)	Nursing home	Nursing home	Home	Home

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Table 4
Characteristics and terminal care management of patients with late-stage Parkinson's disease and a slow trajectory of decline who died at the hospital

		Case 13	Case 14
Patients' demographics	Age (y)	66	82
	Sex	F	M
Parkinson's disease characteristics and treatment	Disease duration (y)	29	Unknown
	Hoehn & Yahr stage	5	5
	Levodopa Equivalent Daily Dose (mg)	Unknown	570
	Current use of LCIG	No	No
	Current use of DBS	Yes (18 years)	No
	Current use of CSAI	No	No
	Apomorphine naïve	Yes	No
	Clozapine (chronic use)	No	No
End-of-life characteristics	Trajectory of decline	Late-stage PD	Late-stage PD (loss of the oral route, hyperalgesic arterial wounds of the lower limbs, infectious pneumonia)
	End-of-life predictors (according to Akbar et al. [12])	Decline in body condition	• Swallowing disorders • falls
	Relevant comorbidities (cancer, organ failure)	N/A	Ischemic stroke, chronic lymphocytic leukemia
	Withdrawal from oral dopaminergic medications	Yes/Unknown duration	Yes/documented/7 days
	Nil by mouth (at the time of evaluation)	Yes	Yes
CSAI as terminal care	Decision to initiate CSAI	Neurologist+PC specialist	Neurologist+PC specialist
	Place of CSAI initiation	PC unit	LTCF then PC Unit
	Clinical condition before CSAI initiation	• Hypertonia • Pain • Swallowing disorders	• Patient bedridden and in pain • Marked axial and segmental rigidity • No longer able to communicate or to take his medications • Hyperthermia • Leukocytosis
	Apomorphine dose (initial and final)	1 mg/h up to 3 mg/h over 24h	1 mg/h up to 3 mg/h during the day and 1.5 mg/h during the night
	Clinical condition after CSAI initiation	• Reduction of hypertonia during nursing care • Relaxed facial expression • Pain relief (hetero-evaluation by the care team and husband)	• Decrease of the akineto-rigid syndrome and pain • Improvement of communication abilities
	CSAI duration	20 days	7 days
	CSAI side effects	Cutaneous (inflammatory infusion sites)	None reported
	CSAI-induced clozapine initiation	No	No
	CSAI-induced domperidone initiation	No	No
Terminal management	Palliative sedation	No	No
	Scopolamine	No	40 mg/24 h IV
	Opiates	Morphine 4.8 mg/day	Morphine up to 56 mg/day
	Benzodiazepines	Midazolam IV 0.2 mg/h	Midazolam 0.3 mg/h during the day 0.4 mg/h during the night
	Others	N/A	Ketamine IV 48 mg/day
	Place of death	PC unit	PC Unit

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systematically involved to ensure PD evaluation, optimal use of infusion material, provide skin care, and monitor CSAI-related side effects.

In all cases, neuropalliative assessment leading to the initiation of low dose CSAI (0.5 up to 3 mg/h/24-h) rapidly and dramatically alleviated PD symptoms, improving patient comfort and facilitating nursing care. Five patients were able to communicate again with their relatives until death. No patient suffered from any behavioral manifestations (visual hallucinations, psychosis, or terminal agitation).

All patient died peacefully without the need for palliative sedation, and half of the patients received terminal care at home.

DISCUSSION

This retrospective cohort illustrates the potential usefulness of a low-dose, 24-h CSAI for symptom management in the context of PD terminal care. Patient identification, non-oral PD therapy choice and CSAI practical management in the broader context of PC remain crucial issues.

The baseline profile of our patients was representative of LSPD [1], with i) diffuse PD phenotype, ii)$\geq$1 prognostic predictors relevant to end-of-life PC [12], iii) acute (infection, surgery) or chronic (cancer, altered general condition) factors precipitating terminal decline, and iv) compromised oral route.

In line with a previous report [10] and owing to its pharmacological properties [14, 15], apomorphine was indicated for symptoms relief (both during day and night [16]) and administered as a 24-h infusion to optimize patient's comfort while avoiding repeated injections, deemed unsuitable in this context. Less invasive than the intravenous route, the subcutaneous route is widely used in PC, especially in the terminal phase, with good safety [17]. In our case, only one injection site per day was required, allowing its use in outpatient settings with good end-of-life quality of care.

Interestingly, low doses of CSAI ($\leq$3 mg per hour on 24 h) were sufficient to improve patient comfort. The context of terminal care may partly account for these low dopaminergic requirements, as most of the patients were bedridden, had suffered weight loss in the previous weeks/months and may have suffered from organ failure, leading to pharmacodynamic and pharmacokinetic changes [18]. Importantly, CSAI was well tolerated, without triggering or worsening neuropsychiatric symptoms, regardless of the previous dopaminergic oral regimen, and even in the case of a previous intolerance at higher dose (patient 4). The short period of time between CSAI initiation and death in all patients (mean duration of 13.9 days), and the previous exposure to clozapine in some patients may have favored good tolerance of apomorphine. In the 7 patients with an acute trajectory of decline (Tables 1 and 2), the mean CSAI duration of 6.1 days (<1–10 days) was similar to the previously described neurological terminal phase duration (8.8 days) [19]. Thus, CSAI seems to improve patient comfort without prolonging survival. For the seven patients with a slow trajectory of decline and swallowing disorders as the main indication for CSAI (Tables 3 and 4), treatment lasted from a few days to a few weeks and prevented or compensated the occurrence of withdrawal syndromes [6, 8], suggesting a possible new indication [14] as part of an advance care planning perspective.

Classic PC medications (scopolamine, opiates, and/or benzodiazepines) were not required in all patients, probably due to a good symptomatic control. Midazolam was used for its anxiolytic properties and not for palliative sedation[1]. Opioid analgesics were used at low dose, mostly to relieve pressure sore-related or cancer-related pain. Antipsychotics as antiemetics were not prescribed in this cohort. In line with recent data highlighting that both sublingual and subcutaneous apomorphine can be initiated without antiemetic pretreatment when using a slow titration scheme [20–22], only one patient experienced nausea, successfully relieved by domperidone. To be noted, palliative sedation was not needed, which may underline the potential interest of CSAI as part of the spectrum of good clinical practice in PD terminal care regarding patient comfort and quality of death. Practical advice on how to implement this therapy (including advised dosing regimen) are summarized in Box 1.

Limitations

As an uncontrolled, real-life, retrospective study, this work presents inherent limitations: a small sample size and clinical assessment based on medical files.

[1] Or continuous deep sedation until death as defined by French Act n° 2016-87 of February 2, 2016, known as the Clayes Leonetti law.

Box 1: Five pragmatic tips on how to initiate apomorphine infusion to improve patient comfort in PD terminal care.

- Based on a neuropalliative care approach, focused on end-of-life quality and multidisciplinary care (preferred apomorphine prescribers: movement disorders specialist, general neurologist; possible apomorphine prescribers with neurological support as needed: palliative care specialist, geriatrician, general practitioner . . .)
- Outpatient or inpatient initiation, using apomorphine infusion pump or classic syringe pump and available subcutaneous apomorphine formulations (vial or solution for infusion in cartridge)
- Prophylactic treatment with an antiemetic (domperidone) is not mandatory. Neuroleptics (e.g., metoclopramide, metopimazine) are not to be used
- PD nurse supervision (mandatory at first and then as needed) to ensure PD evaluation, optimal use of infusion material, provide appropriate skin care, and monitor CSAI-related side effects
- Advised dosing regimen: start at 0.5 mg/h/24-h and increase with daily increments of 0.5 mg/h until clinical relief (rigidity, pain) and patient comfort are obtained

Conclusion

At the intersection of palliative medicine, geriatric medicine, and neurology, LSPD patients' terminal care management requires a transdisciplinary approach [2–4]. CSAI may be of great interest in this context, regardless of the trajectory of decline, as it reduces motor symptoms and overall discomfort, with an apparently good safety profile. Level of palliative medication in our series was comparable or below those in other end-of-life PD cohorts [9, 11], which reinforces the idea that apomorphine does not cause excessive symptoms in this population. Use of the apomorphine pen, sublingual film or of a classic syringe pump could be considered when apomorphine infusion pumps are not available.

Considering that management was satisfactory in this cohort in both inpatient and outpatient care, CSAI use deserves to be considered in different settings, notably in an advance care planning perspective. Larger observational cohorts and randomized controlled trials are needed to establish its efficacy and safety in the context of neuropalliative care.

ACKNOWLEDGMENTS

The authors wish to thank the Adelia® care team (notably Régis Bouillot, Morgane Bérée & Séverine Autret), Régis Aubry, Héloïse Chassier, Adélaïde Müller, the Asten® care team (notably Mickaël Chapuis & Isabelle Martin) and all the clinicians who participated in taking care of the patients in different settings. The authors thank Jennifer Dobson for proofreading the manuscript. Finally, MA, MB, MG, and MV also wish to thank France Parkinson and Plateforme Nationale pour la Recherche sur la fin de vie for supporting their different projects related to palliative care in Parkinson's disease (APO-PALLIA project & SPARK network). The preliminary results of this study have been presented as a poster at the 74th American Academy of Neurology annual meeting (AAN, Seattle, USA), at the 2022 International Congress of Parkinsons's disease and movement disorders (MDS, Madrid, Spain), at the 2022 virtual congress of the International Neuropalliative Care Society (INPCS) and at the 2023 World Parkinson's Congress (WPC, Barcelona, Spain).

FUNDING

The authors have no funding to report.

CONFLICT OF INTEREST

MB reports grants from France Parkinson, Plateforme Nationale pour la Recherche sur la Fin de Vie, reimbursement of travel expenses to scientific meetings from Asten, Boston Scientific, Elivie, Orkyn and Medtronic, honoraria from Abbvie, Aguettant, Allergan, Merz Pharma, Orkyn for lecturing outside the submitted work.

MG reports travel grants and speaker honoraria from Aguettant, and research grant from Plateforme Nationale pour la recherche sur la Fin de Vie.

GD reports one travel grant from Mundipharma.

LT reports honoraria from Allergan, Merz Pharma and Ipsen.

MV served on scientific advisory boards, received research support and received travel grant from Aguettant, Adelia Medical, Asdia, Britannia Pharmaceutical Ltd, Elivie, LVL, France Parkinson, Plateforme Nationale pour la Recherche sur la Fin de Vie, Orkyn.

MA reports travel grants, speakers & consultancy honoraria and/or research grants from France Parkinson, Plateforme Nationale pour la Recherche sur la Fin de Vie, Institut des Neurosciences Cliniques de Rennes, Aguettant, Britannia Pharmaceutical Ltd, Adelia Medical, Linde Homecare, Homeperf, Asdia, Orkyn, France Développement Electronique & Society for Dental Science. Dr Auffret is employed by France Développement Electronique (FDE) and

works as a hosted researcher at the Pontchaillou University Hospital & University of Rennes.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article.

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