Neurological Sciences (2019) 40:1917–1923
https://doi.org/10.1007/s10072-019-03920-5

ORIGINAL ARTICLE

Continuous subcutaneous apomorphine infusion in Parkinson's disease: causes of discontinuation and subsequent treatment strategies

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Received: 22 December 2018 / Accepted: 2 May 2019 / Published online: 20 May 2019

Abstract

Continuous subcutaneous apomorphine infusion (CSAI) is a well-recognized therapeutic option for the management of motor fluctuations in Parkinson's disease (PD), although clinical experience suggests that most patients discontinue CSAI after a variable amount of time due to several causes and circumstances. The objective of the present study was to evaluate the reasons of CSAI discontinuation and to investigate which treatment was adopted afterwards. Two independent raters retrospectively reviewed the electronic medical record of 114 patients treated with CSAI for at least 6 months. The records were reviewed regarding efficacy, safety, and evolution of CSAI treatment. Most of PD patients on CSAI had a significant improvement in their clinical condition. Lack of improvement of dyskinesia was the most frequent causes of treatment discontinuation. The second reason for CSAI discontinuation was cognitive deterioration. At CSAI discontinuation, younger patients were more likely to undergo deep brain stimulation (DBS), while older patients and patients with cognitive impairment were more likely switched to oral therapy alone (OTA). CSAI is an effective treatment that unfortunately must be discontinued in a great number of patients with advanced PD. As older age is the main limiting factor for accessing second-level therapies at CSAI discontinuation, CSAI treatment should not be postponed to older age. CSAI might be considered a good first-line and fast strategy in patients undergoing rapid deterioration of their quality of life while waiting for DBS or levodopa/carbidopa intestinal gel therapy.

Keywords Apomorphine · DBS · Dyskinesia · Parkinson's disease

Introduction

The management of advanced Parkinson's disease (PD) is often complicated by the occurrence of severe motor complications [1, 2]. In the last years, several therapeutic options have been introduced in order to improve motor complications, including deep brain stimulation (DBS) of either subthalamic nucleus (STN) [3–5] or globus pallidus (GPi) [6] as well as continuous dopaminergic stimulation by means of either administration of levodopa/carbidopa intestinal gel (LCIG) [7–10] or continuous subcutaneous apomorphine infusion (CSAI) therapy [11–13].

Apomorphine is the most potent dopamine agonist available to date; however, due to the poor oral bioavailability and short half-life, it can only be administered subcutaneously as acute injections (pen-jet) or with a micropump for continuous subcutaneous infusion [14]. Several previous studies showed that CSAI improves motor fluctuations and dyskinesia in advanced PD patients, also allowing levodopa dose reduction [15–20]. In spite of these benefits, clinical experience suggests that most patients discontinue CSAI after a variable amount of time due to loss of efficacy or the occurrence of troublesome side effects, such as subcutaneous nodules, sedation, gastrointestinal (GI) symptoms (i.e., nausea and vomiting), renal impairment,

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orthostatic hypotension, psychosis, mood disorders, and—more rarely—cardiovascular complications (arrhythmias) or hemolytic anemia [21–25].

So far, only few studies have been conducted to evaluate the causes and circumstances of CSAI discontinuation and which treatment is more likely adopted after CSAI withdrawal. Understanding these factors may improve our knowledge on the ideal patient's profile for CSAI. For this purpose, we retrospectively reviewed the available data on the efficacy, safety, and evolution of CSAI treatment in a large cohort of PD patients followed in our Movement Disorder Center.

Methods

Study design

This is a retrospective, open-label, observational cohort study involving 143 patients treated with CSAI for at least 6 months in the period from January 1998 to December 2012 and who discontinued the infusion for adverse events. The electronic medical records of the Parkinson Center at Neuromed Institute (Pozzilli, IS, Italy) were reviewed by two independent researchers (NM, FL). Out of the initial cohort, 114 patients with no missing data where included in the final analysis.

Demographic data and clinical assessments

Demographic and clinical data recorded were gender, age, age at disease onset, body side of onset, disease phenotype (tremor-dominant or rigid-akinetic), age at CSAI onset, and CSAI treatment duration. Patients' cognitive state was assessed by means of Mini-Mental State Examination (MMSE) collected before and after apomorphine infusion treatment. PD severity and effect of apomorphine infusion were evaluated through the Clinical Global Impression (CGI) scale [26] based on physician's notes during the whole observation period. Raters, independently assessed severity (CGI-S) at onset of apomorphine infusion and improvements (CGI-I) at the last observation prior to apomorphine discontinuation. CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (CGI-S ratings from 1 = normal to 7 = extremely ill). CGI-I is another 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention (CGI-I ratings from 1 = very much improved to 7 = very much worse). Motor status and motor complications of patients were assessed at the time of CSAI introduction with Unified Parkinson's Disease Rating Scale (UPDRS) part III during "on" state and UPDRS part IV [27].

We determined the causes of CSAI discontinuation and reported the treatment after therapy discontinuation.

Statistical analysis

We first performed a descriptive statistical analysis to obtain demographic information of the sample. Inter-rater reliability on CGI evaluations was calculated through Cohen's kappa measure. The cohort was then stratified for age at CSAI onset (above or below 70 years), and the two groups were compared using chi-squared tests for categorical parameters and Student's t test for ordinal ones. Causes of discontinuation from CSAI treatment were recorded for safety monitoring, and prevalence of each of them was calculated.

As a second step of analysis, we divided the cohort in three groups depending on the treatment introduced at CSAI discontinuation, namely, DBS, LCIG, or oral therapy alone (OTA). Differences in clinical features of patients in these three groups were investigated through ANOVA and the Bonferroni post hoc test. Survival tables were used to characterize the temporal profile of CSAI discontinuation; the log rank test was used to compare them according to the principal clinical features, which were categorized according to a cut-off value representing their median value or presence of intact cognition (defined as a MMSE score of 30).

A logistic regression analysis was finally used to discover the best clinical predictors of treatment after CSAI. Analyses were conducted with SPSS 14.0 and the significance threshold was set at $p = 0.05$.

Results

Demographics and CGI evaluation

Clinical and demographic characteristics of patients are detailed in Table 1. The period of CSAI treatment ranged between 0.5 and 9.2 years with a mean of 2.42 years. At the time of CSAI onset, none of the patients had MMSE scores lower than 25. Cohen's kappa measure between the two raters of CGI-S was 0.63. Based on the CGI-S, all patients who underwent CSAI treatment were markedly or severely ill.

We did not find any gender effect on disease duration at CSAI onset, age at CSAI onset, MMSE score at treatment onset and discontinuation, and CGI-S and CGI-I scores. At the last observation performed prior to CSAI discontinuation, clinical improvement ranged between "very much improved" and "much improved" in 94 patients (82.45%), with 17 patients (14.91%) minimally improved and 3 patients unchanged. MMSE mean score significantly decreased after CSAI treatment ($p < 0.001$), with no difference according to phenotype and side of disease onset; specifically, 15% of patients scored below 24 and 4.6% scored between 10 and 21.

Table 1 Demographic and clinical features of the 114 enrolled patients

	Mean ± SD (range) or *N* (%)
Age	68.3 ± 9.48 (44–87)
Male/female	69/45 (60.5%/39.5%)
Age at PD onset	59.3 ± 9.16 (37–78)
Side involved at PD onset: right/left	59/55 (51.8%/48.2%)
Motor phenotype: rigid/tremor-dominant	65/40 (57.0%/43.0%)
UPDRS III ("on" state)	19.12 ± 6.41 (7–39)
UPDRS IV	5.69 ± 3.19 (2–16)
CSAI treatment duration (years)	2.42 ± 2.23 (0.5–9.2)
CGI-S	5.17 ± 0.38 (5–6)
CGI-I	2.16 ± 0.7 (1–6)
MMSE at treatment onset	29.58 ± 1.06 (25–30)*
MMSE at treatment discontinuation	28.2 ± 3.12 (10–30)*

SD standard deviation, *PD* Parkinson disease, *UPDRS* Unified Parkinson's Disease Rating Scale, *CSAI* continuous subcutaneous apomorphine infusion, *CGI-S* Clinical Global Impression-Severity, *CGI-I* Clinical Global Impression-Improvement, *MMSE* Mini-Mental State Examination

*Significantly different ($p < 0.001$)

Stratifying the cohort depending on age at CSAI onset, we found that 63 patients started CSAI before the age of 70 (mean = 61.3 ± 6.4) and 51 patients at the age of 70 or above (mean = 76.6 ± 4.5). These two groups did not differ in terms of gender, CSAI duration and efficacy (based on the CGI-I scores), and MMSE score at baseline and discontinuation. The two groups, however, differed in terms of disease severity as the group age above 70 years showed worse UPDRS ($p = 0.003$) and CGIS ($p = 0.004$) scores.

Reasons for CSAI discontinuation

The rate of CSAI treatment discontinuations and the main reasons leading to it are shown in Fig. 1. The most frequent cause of discontinuation was the lack of dyskinesia improvement (36.8%). Treatment duration was significantly longer in these patients ($p = 0.019$). Patients who discontinued CSAI due to worsen of cognition were significantly older than patients who discontinued CSAI for other reasons ($p = 0.023$). Patients with higher CGI-I scores had higher prevalence of hypotension, dyskinesia, and psychiatric complications as causes of discontinuation ($p < 0.005$). When comparing CSAI survival according to the principal clinical features, only the severity of motor fluctuations (based on UPDRS-IV) was associated with an earlier treatment discontinuation (log rank 67.294, $p < 0.0001$; Fig. 2).

Switch to other therapies

At CSAI discontinuation, patients were switched to the following therapies: 34 patients (29.82%) underwent STN DBS, 16 patients (14.03%) started LCIG, and 64 patients (56.14%) went back on OTA. The clinical differences of these three groups are shown in Table 2.

The logistic regression showed that young age at PD onset predicted the switch to STN DBS ($p < 0.001$), while the switch to OTA was better predicted by older age at CSAI discontinuation ($p = 0.004$) and by MMSE score at CSAI discontinuation ($p = 0.02$).

Discussion

This large retrospective observational study confirms that CSAI is an effective treatment for complicated PD. Based on the CGI-I evaluation, majority of patients had a significant improvement in their clinical condition. In keeping with a large amount of literature, all patients were markedly or severely ill at the time of CSAI introduction [12, 14, 15, 25]. These findings are in keeping with the OPTIPUMP study, which showed that CSAI had a favorable impact on the patients' quality of life, without worsening of the hyperdopaminergic behaviors [28].

The mean of CSAI treatment duration of the cohort was 2.42 years, ranging between 0.5 and 9.2 years and showing that CSAI is a well-tolerated treatment in the mid- and even in the long-term period. The long treatment duration of our study allowed the analysis of an aspect still not fully investigated, namely, the reason and timeline of CSAI discontinuation. In line with similar studies conducted on LCIG therapy [29], the most common reason for CSAI discontinuation was the lack of improvement of dyskinesia over time, as also confirmed by our survival analysis (Fig. 2). Previous studies reported no worsening [25] or improvement of dyskinesia probably due to concomitant levodopa dose reduction [15]. Unfortunately in our study, we do not have enough data to discuss the lack of efficacy on dyskinesia over time. Probably, in the patients that interrupted CSAI for lack of control of dyskinesia, the initial improvement was lost for levodopa pulsatility in concomitance with CSAI and a combination of factors that include alterations in signaling at many neurotransmitter receptors, abnormal synaptic plasticity and altered firing pattern, and synchronicity in the basal ganglia circuit [30, 31]. Cognitive deterioration over time, during CSAI treatment, was the second reason for discontinuation in our population. Of note, while none of the patients reported a MMSE score below 25 at CSAI onset, at CSAI discontinuation, 15% of patients scored below 24 and 4.6% scored between 10 and 21, with no difference in gender. We postulated that the worsening of cognitive state could be due to a faster rate of disease progression or older age of patients rather than to CSAI itself. However, in these patients, we decided to discontinue apomorphine because patients with cognitive impairment are at higher risk for development of neuropsychiatric side effects following

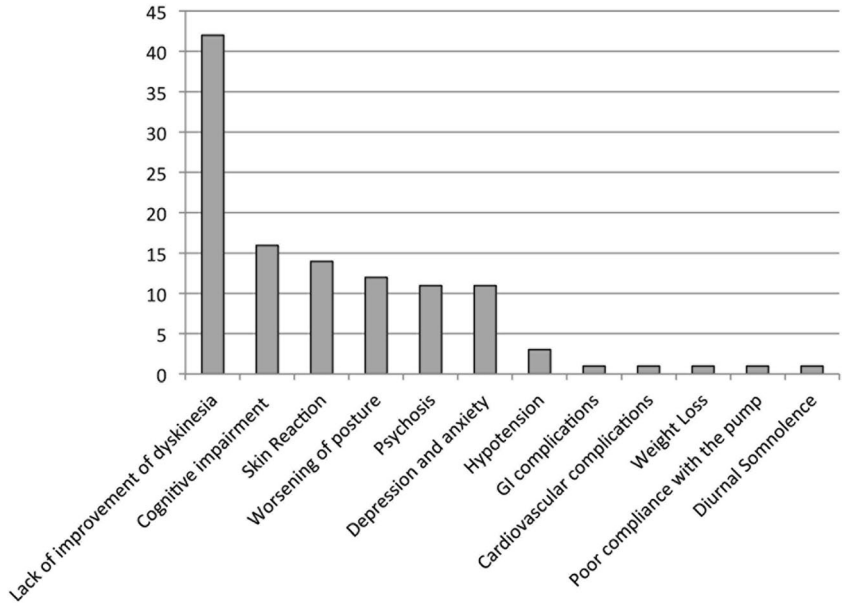

Fig. 1 Reasons for CSAI discontinuation

treatment with CSAI [12]. Nevertheless, the effect of CSAI on cognition is still unclear: previous studies reported a worsening of cognitive state [25, 32], whereas other studies reported that CSAI does not worsen cognition [20, 33–35]. We can only suggest that it could be useful to monitor the cognitive status during the treatment period. Other minor causes of

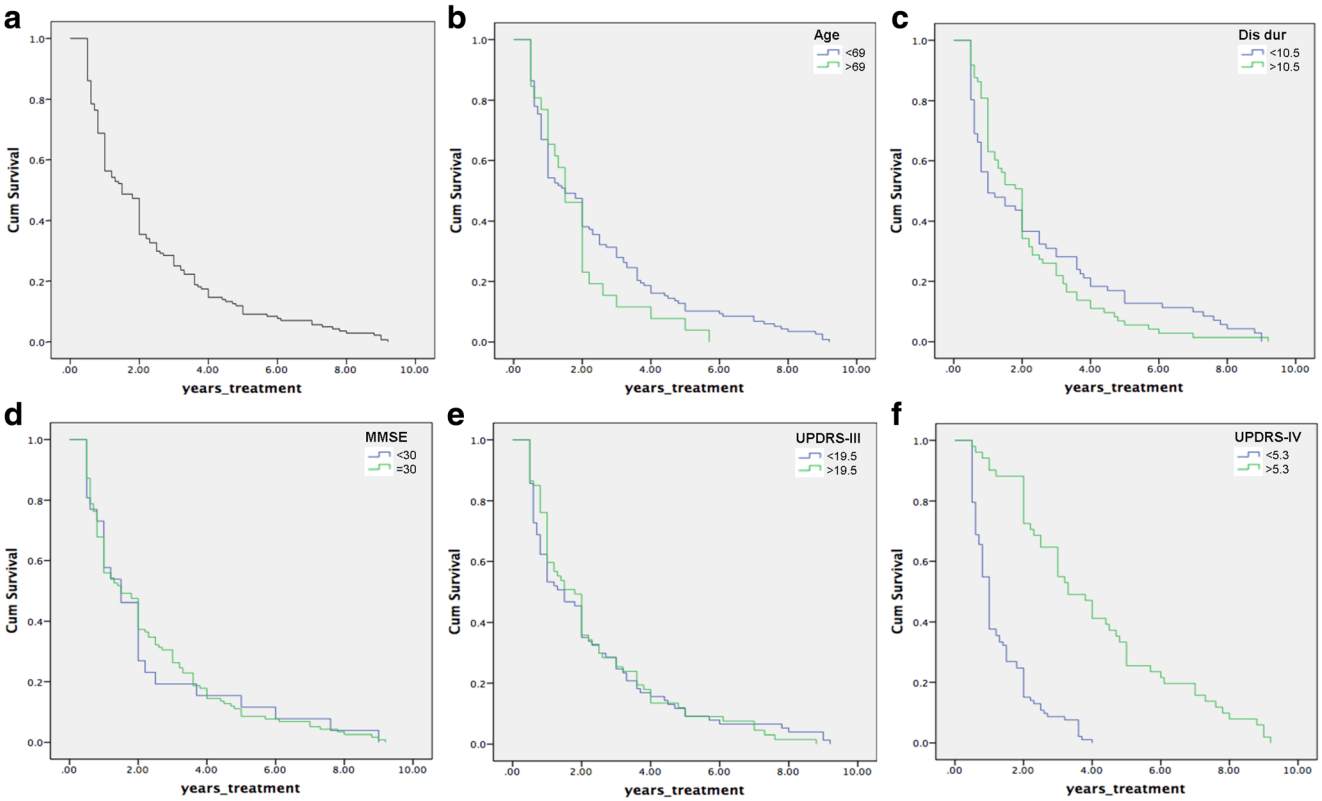

Fig. 2 Survival tables were used to characterize the temporal profile of CSAI discontinuation in the entire cohort of patients (**a**) and when stratifying them according to age at CSAI initiation (**b**), disease duration at CSAI initiation (**c**), intact vs. impaired cognition based on MMSE at CSAI initiation (**d**), motor impairment at CSAI initiation based on UPDRS-III on medication (**e**), and severity of motor fluctuations at CSAI initiation based on UPDRS-IV (**f**). The log rank test was used to compare the impact of the aforementioned features on timing of discontinuation: severity of motor fluctuations was the only significant factor (log rank 67.294, $p < 0.0001$). Abbreviations: dis durat, disease duration expressed in years; MMSE, Mini-Mental State Examination

Table 2 Clinical features of patients according to the treatment after CSAI

	OTA ($n = 58$)	DBS ($n = 34$)	LCIG ($n = 16$)	Oral vs. DBS	DBS vs. LCIG
Age at PD onset	50 ± 1.6 (31–68)	42.16 ± 1.55 (33–58)	49.75 ± 1.9 (31–60)	< 0.001	0.029
Age at CSAI onset	61.37 ± 1.22 (41–78)	55.29 ± 1.34 (37–67)	60.75 ± 2.11 (44–74)	0.005	NS
CSAI duration	2.29 ± 0.29 (0.5–9)	2.39 ± 0.36 (0.5–9.2)	3.6 ± 0.61 (0.5–8)	NS	NS
MMSE pre-CSAI	29.35 ± 0.16 (25–30)	29.94 ± 0.58 (28–30)	29.62 ± 0.27 (26–30)	0.033	NS
MMSE post-CSAI	27.7 ± 0.51 (10–30)	29.35 ± 0.21 (25–30)	27.18 ± 0.61 (22–30)	NS	NS
CGI-S	2.01 ± 0.83 (1–4)	2.29 ± 0.89 (2–4)	2.43 ± 0.27 (1–6)	NS	NS
CGI-I	5.17 ± 0.005 (5–6)	5.14 ± 0.61 (5–6)	5.31 ± 0.11 (5–6)	NS	NS

Data are expressed as mean ± SD (range)

OTA oral therapy alone, *DBS* deep brain stimulation, *LCIG* levodopa/carbidopa intestinal gel, *PD* Parkinson disease, *CSAI* continuous subcutaneous apomorphine infusion, *MMSE* Mini-Mental State Examination, *CGI-S* Clinical Global Impression-Severity, *CGI-I* Clinical Global Impression-Improvement

CSAI discontinuation were skin reactions, worsening of posture, and neuropsychiatric effects, including psychosis such as hallucinations and mood disturbances such as depression and anxiety.

In clinical trials, the most common reported side effects, in up to 70% of patients treated with CSAI, were local skin nodules at the injection site. In 10–20% of patients, necrotic ulcerations of the nodules or panniculitis can occur [36, 37].

Several papers have addressed the effect of apomorphine on neuropsychiatric symptoms and found that apomorphine infusion is well tolerated in patients experiencing visual hallucinations and paranoid ideations [38] and is correlated with a significant improvement of mood evaluated by the Beck Depression Inventory [39]. Ellis et al. even reported a reduction in hallucinations experienced by 12 non-demented patients receiving CSAI as they were able to reduce their oral antiparkinsonian medication [38]. Unfortunately, we cannot discuss the reason why the patients of our study interrupted the treatment for neuropsychiatric complications for the study limitations. However, we can only speculate that this small number of patients (11 patients with psychosis and 11 with mood disorders) was probably developing neuropsychiatric symptoms for disease evolution or increasing the antiparkinsonian medications over time.

Furthermore, few reports have described postural abnormalities mainly related to dopaminergic therapy in PD patients [40, 41].

Our study focused also on what is next after CSAI discontinuation. We found that half of the cohort was switched to OTA, about 30% to DBS and the rest to LCIG. As showed by the logistic regression, the older patients and the patients with worse MMSE scores were more likely switched to OTA; on the other hand, young-onset PD patients were more likely switched to DBS. This observation is in keeping with current standard practice and what is recommended by available guidelines [42].

The observations here reported raise the following questions: what is the clinical profile of the ideal CSAI candidate, and what is the ideal CSAI treatment duration to keep the best trade-off between benefits and complications of the therapy.

In our opinion, CSAI should be proposed to patients with complicated forms of the disease, as the improvement observed in this study was indeed higher in patients with more severe motor fluctuations. In addition, we believe that CSAI introduction should not be postponed to older age, as older age is the main limiting factors for accessing second-level therapies at CSAI discontinuation. Furthermore, older patients might be at higher risk of cognitive deterioration following CSAI introduction.

Our findings suggest that CSAI should not be considered a definitive treatment for patients but certainly a good "bridge" therapy between oral treatments and advanced therapies. Sesar et al. [25], indeed, have recently shown that apomorphine could be a useful strategy to manage the DBS waiting list. To this respect, it is worth mentioning that CSAI is easily implementable without hospitalization and it is easily reverted, as no surgical procedure is needed to start the treatment. CSAI should be therefore considered a first-line and fast strategy in patients undergoing rapid deterioration of their quality of life while waiting for DBS or LCIG.

This study suffers from several and important limitations to be acknowledged. First of all, this is a retrospective and open study, although the use of two independent raters of clinical data proved to be effective, also according to the good inter-rater agreement. More importantly, we were not able to recollect enough information on apomorphine main infusion dose in the cohort over the period of observation or the mean difference in levodopa daily dose after CSAI introduction. Even though the best possible titration of apomorphine was attempted in all patients, we cannot exclude that the magnitude of levodopa reduction was not optimized with an impact of timing and causes of discontinuation. A recent study, indeed, showed that the magnitude of levodopa reduction, estimated in about 20%, seems to be a positive predictive factor on the duration of CSAI [43].

Conclusions

In conclusion, our study, although with several limitations, confirms that CSAI can be used as a temporary treatment of advanced PD in well-selected patients.

The effect on motor symptoms is significant for the first period, after which follow-ups are very important to determine eventual lack of motor efficacy and presence of side effects or of non-motor symptoms probably due to PD progression that can induce CSAI withdrawal.

Acknowledgments We are grateful to Dr. Antonella Conte for reviewing the database.

Compliance with ethical standards

Conflict of interest Drs. Fasano and Modugno received speaking honoraria from Chiesi pharmaceutical, distributor of apomorphine in Italy. The remaining authors have no conflict of interest.

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