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Short communication

Early factors for predicting discontinuation to subcutaneous Apomorphine infusion in Parkinson's disease: A prospective analysis of the Thai Apomorphine Registry

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ABSTRACT

Introduction: Although continuous subcutaneous apomorphine infusion (CSAI) is an effective therapy for Parkinson's disease (PD) with motor fluctuations, data from Asian cohorts is limited. The therapy is often discontinued due to the complexity of its delivery.
Methods: Fifty-one PD patients undergoing CSAI as an add-on therapy were enrolled in the Thai Apomorphine Registry, an electronic database that recorded clinical characteristics and parameters during the 14-consecutive-day titration and long-term follow-up. Factors at the time of titration were documented in order to identify predictors of long-term discontinuation.
Results: Following initiation, PD patients were administered a mean CSAI dose of 5.89 mg/h (SD 1.36) over a mean time of 12.28 h (SD 1.90) each day. The mean follow-up period was 626.2 days (SD 619.17). Significant reductions in UPDRS-I, II, III, and IV scores, total NMSQ score, PDQ-8 score, daily off and dyskinesia hours, Timed Up and Go test, walking step test, levodopa-equivalent daily dose, number of times a day the levodopa was taken versus pre-CSAI values were observed ($p < 0.05$, each). Thirty-five (68.6%) patients discontinued during the follow-up period. Relative risks of variables recorded at the time of titration that determined discontinuation of CSAI therapy were an absence of full-time caregivers, achieving a daily off hours reduction <3.5 h, and NMSQ scores at the time of CSAI titration ≥ 9.5 points.
Conclusion: Identifying factors that predict discontinuation of CSAI at the time of its initiation may help physicians to better understand the patient's drug response and how to manage them long-term.

1. Introduction

Continuous subcutaneous apomorphine infusion (CSAI) is a well-established and effective add-on therapy for advanced Parkinson's disease (PD) with disabling motor fluctuations [1]. Using continuous drug delivery systems, CSAI offers major reductions in motor complications, particularly in PD patients with both motor and nonmotor fluctuations, while providing benefits to both types of symptoms [2]. A recent randomized controlled trial confirmed the significant benefit of CSAI in off hours reduction without any unexpected safety events, compared to a placebo [1]. Observational studies have also reported long-term benefits of CSAI lasting up to 10 years following treatment [3–5]. Compared to other device-aided therapies, including levodopa-carbidopa intestinal gel infusion and deep brain stimulation, CSAI is the least invasive drug administration procedure and is easily reversible, whereas the other two options require further surgery for reversal [6]. Despite the growing evidence for CSAI benefits in PD, there are relatively few cohorts of Asian patients to demonstrate its efficacy in this population [7]. In addition, the delivery process of CSAI and the complexity of the delivery system mean that up to 60% of patients discontinue CSAI over the

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long-term [7]. Therefore, there is a need for an Asian cohort study to demonstrate CSAI efficacy and identify variables at the initiation of therapy that can predict long-term discontinuation of CSAI. This information should help physicians to better understand a patient's drug response and identify early which patients may discontinue CSAI in order to support and manage their long-term therapy effectively.

Though not approved by the Thai FDA until 2015, CSAI was first used in Thailand in 2013 for compassionate use in seven PD patients with medically intractable motor fluctuations. The Apomorphine Registry was established after this date by the Chulalongkorn Centre of Excellence for Parkinson's Disease and Related Disorders (ChulaPD, www.apomorphineregistry.org), which is the lead centre for registering patients in Thailand (Fig. S1). This Registry exclusively included patients undergoing CSAI as an add-on therapy. The main objective for establishing the registry was to collect patient information and other CSAI-related outcomes to help neurologists determine whether appropriate healthcare services and assistance were accessible to patients with CSAI and their caregivers [6]. The data collection comprised of two periods (Fig. S2): 1) a 14-consecutive-day CSAI initial titration and 2) long-term follow up of CSAI therapy. In this study, we reported a description of the initial results of the Thai Apomorphine Registry, namely the 14-consecutive-day initial CSAI titration to verify its efficacy amongst Thai PD patients. However, factors at the time of CSAI titration are also reviewed in order to identify predictors of long-term discontinuation of CSAI therapy.

2. Methods

2.1. Participants and procedures

During October 2013 to November 2020, 89 degenerative parkinsonism patients received CSAI in Thailand. Eighty-five (95.9%) of them were diagnosed with advanced PD with motor complications, and of these 51 patients completed this cohort study. Details of patient recruitment are shown in Fig. S2. A comprehensive electronic database was created for prospectively recording patient characteristics and clinical parameters from the 14-consecutive-day CSAI initial titration and long-term follow up of CSAI therapy. So far, the maximum follow-up period in this study is 7 years. The protocol for CSAI titration was previously established by our group [8]. During CSAI initial titration, patients visited the hospital at baseline and every consecutive weekday for 14 days to assess the clinical efficacy and any unfavourable outcomes. Four types of patient's outcomes were assessed and rated according to either standard clinical rating scales and/or objective tools including, 1) motor outcomes, 2) non-motor outcomes, 3) activity of daily living (ADL) and quality of life (QOL) outcomes, and 4) complication of treatment outcomes. Motor outcomes were rated at baseline and hourly until the last day of titration by neurologists or trained PD nurse specialists using the following: 1) clinical rating scales, including the Unified Parkinson's Disease Rating Scale – motor section (UPDRS III) and Hoehn and Yahr stage (HY); 2) electronic PD diary; 3) daily off hours and daily dyskinesia hours, and 4) objective measurements, consisting of finger tapping test, Timed Up and Go test, and walking step test [8]. The finger tapping test documents the number of finger taps for each hand in 1 min. The walking step test documents the number of walking steps while performing TUG. Videos of patients' performance during these assessments were also recorded for future analysis. Non-motor outcomes were rated at baseline and the last day of CSAI titration using the following: 1) Mini-mental state examination (MMSE); 2) UPDRS-mentation, behavior, and mood section (UPDRS I); and 3) Non-motor symptoms questionnaire (NMSQ), a 30-Item questionnaire separated into 9 non-motor domains including digestive (7 items), urinary (2 items), memory (3 items), hallucination (2 items), depression (2 items), sexual (2 items), cardiovascular (2 items), sleep (5 items), and miscellaneous (5 items) [9]. ADLs were rated at baseline and the last day of titration using UPDRS-activities of daily living section (UPDRS II). Health-related QOL was rated at baseline and the last day of titration using the 8-item Parkinson's disease questionnaire (PDQ-8). In addition, complication of treatment was rated at baseline and the last day of titration using UPDRS complications of therapy section (UPDRS IV).

After completing CSAI titration, patients who continued CSAI usage were recruited for the long-term follow-up period. During this period, all data continued to be obtained on a regular basis until the enrolled patient discontinued CSAI, regardless of the reason. In addition, we documented the time and reasons for discontinuation of CSAI to identify factors recorded at the time of CSAI titration that may be predictive of discontinuation of the therapy. The study protocol was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB 647/63). Information regarding this research study was provided and written informed consent was obtained from every subject at enrollment, in accordance with the declaration of Helsinki.

2.2. Statistical analysis

Patient characteristics and clinical parameters are presented as the mean ± standard deviation or number (percentage). Parametric and non-parametric tests were as appropriate. The Shapiro-Wilk statistic was calculated to determine the normality of data to the p value. Paired-sample T test was used to compare continuous data between before and during CSAI. Mann-Whitney U test was used to compare continuous data between continued users and discontinued users. Examination of the receiver operating characteristic (ROC) curve was used to assess the cut-off points of variables at the time of CSAI titration that predicted discontinuation of CSAI in the long-term cohort study, as well as specificity and sensitivity. Relative risks were measured to classify variables that predicted the discontinuation of CSAI. To determine statistical significance, we used 95% confidence intervals and the Chi-squared test with continuity correction. Survival functions were analysed using Log rank methods and a Kaplan-Meier plot to determine the effect of the presence of caregivers and continuation of CSAI. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (version 23.0; SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline demographics and patient characteristics

Of the 51 PD patients, 32 (62.7%) were female and 19 (37.3%) were male with mean age at the time of CSAI initiation of 63.53 years (SD 10.35). All patients were diagnosed with PD, mean disease duration of 10.88 years (SD 3.62), and fulfilled a suitable candidate profile for CSAI according to the expert consensus group report [10]. The most common indication for CSAI was severe unpredictable off symptoms in 34 patients (61.8%), followed by complex on-off fluctuations in 14 patients (25.5%), and severe dyskinesia in 7 patients (12.7%). Thirty-six patients (70.6%) had a full-time caregiver. The full demographic results of all participants are shown in Table 1.

3.2. Results of the 14-consecutive-day CSAI initial titration

CSAI was administered as an add-on therapy to patients' existing oral and/or transdermal medications. Comparative results between baseline data and that with CSAI are shown in Table S1. The patients required a mean titration of 10.02 days (SD 3.82). The mean dosage of CSAI was 5.89 mg/h (SD 1.36), administered over a mean time of 12.28 h per day (SD 1.90). Compared to baseline, a significant improvement in patients' symptoms was observed following CSAI. For general outcomes, a reduction in LED, and a reduction in the number of times a day the levodopa was taken were found ($p < 0.05$, each). For motor outcomes, as shown in Fig. 1A, a reduction in daily off hours, a reduction in daily dyskinesia hours, a reduction in UPDRS III, an increase in the number of finger taps on both sides, a decrease in the Timed Up and Go test, and an

Table 1
Comparison of parameters between all users, continuing and discontinued users.

Category	Apomorphine users			*p*-value (continuing vs. discontinued users)
	All users (N = 51)	Continuing users (N = 16)	Discontinued users (N = 35)	
General information				
Age (years)	63.53 ± 10.35	63.63 ± 11.01	63.49 ± 10.19	0.871
Male gender	19 (37.3%)	6 (37.5%)	13 (37.1%)	0.980
Most affected side: Right hand	22 (43.1%)	6 (37.5%)	16 (45.7%)	0.583
Presence of full-time caregivers	36 (70.6%)	16 (100%)	21 (60%)	0.003*
Disease duration (years)	10.88 ± 3.62	10.13 ± 3.14	11.23 ± 3.82	0.262
HY during on period	3.34 ± 0.57	3.12 ± 0.34	3.44 ± 0.62	0.077
The number of titration day (days)	10.02 ± 3.82	9.86 ± 4.68	10.09 ± 3.50	0.841
Maximum dose of CSAI (mg)	5.89 ± 1.36	5.98 ± 1.02	5.85 ± 1.49	0.951
LED at baseline (mg)	1323.99 ± 652.54	1406.14 ± 561.36	1275.45 ± 709.00	0.578
LED with CSAI (mg)	848.68 ± 560.49	857.67 ± 498.81	843.43 ± 603.88	0.520
The number of times a day the levodopa taken at baseline	6.05 ± 1.54	6.54 ± 1.26	5.80 ± 1.63	0.199
The number of times a day the levodopa taken with CSAI	3.89 ± 1.84	4.31 ± 2.13	3.68 ± 1.67	0.484
The number of daily hours with CSAI (hours)	12.28 ± 1.90	12.33 ± 1.05	12.26 ± 2.16	0.170
Motor assessment				
Daily off hours at baseline (hours)	6.16 ± 2.55	7.25 ± 3.45	5.66 ± 1.86	0.130
Daily off hours with CSAI (hours)	1.94 ± 1.39	1.35 ± 1.49	2.12 ± 1.32	0.058
Daily off hours reduction with CSAI (hours)	4.22 ± 2.68	5.72 ± 2.94	3.53 ± 2.28	0.008*
Daily dyskinesia hours at baseline (hours)	4.39 ± 1.98	4.20 ± 1.82	4.46 ± 2.07	0.956
Daily dyskinesia hours with CSAI (hours)	2.58 ± 1.72	2.01 ± 1.52	2.84 ± 1.76	0.051
Daily dyskinesia hours reduction with CSAI (hours)	1.84 ± 2.11	2.19 ± 1.42	1.68 ± 2.35	0.244
UPDRS III: motor section score, off period at baseline	47.37 ± 13.59	43.53 ± 9.06	49.06 ± 14.97	0.143
UPDRS III: motor section score, on period at baseline	29.08 ± 14.01	22.88 ± 8.27	32.09 ± 15.29	0.051
UPDRS III: motor section score, on period with CSAI	21.98 ± 15.31	14.58 ± 6.88	25.57 ± 16.97	0.050*
Percent improvement of UPDRS motor section score with CSAI	26.44 ± 28.91	34.47 ± 27.88	22.55 ± 29.00	0.122
Finger tapping (Right) at baseline	115.50 ± 38.73	123.94 ± 48.23	111.14 ± 32.87	0.351
Finger tapping (Right) with CSAI	154.68 ± 34.43	172.32 ± 32.02	145.86 ± 32.56	0.022*
Finger tapping (Left) at baseline	110.44 ± 38.85	114.23 ± 48.82	108.48 ± 33.32	0.849
Finger tapping (Left) with CSAI	149.97 ± 38.69	164.83 ± 43.96	142.31 ± 33.93	0.082
Finger tapping (most affected side) at baseline	106.44 ± 37.37	110.35 ± 46.82	104.43 ± 32.15	0.719
Finger tapping (most affected side) with CSAI	150.16 ± 36.83	167.50 ± 39.29	147.22 ± 32.64	0.039*
Finger tapping (least affected side) at baseline	119.49 ± 39.22	127.83 ± 49.04	115.19 ± 33.18	0.459
Finger tapping (least affected side) with CSAI	155.23 ± 36.43	169.64 ± 37.97	147.79 ± 33.85	0.056
Timed Up and Go test at baseline (sec)	15.55 ± 10.11	14.33 ± 5.60	16.41 ± 12.38	0.662
Timed Up and Go test with CSAI (sec)	11.71 ± 5.01	11.89 ± 5.75	11.59 ± 4.59	0.905
Walking step test at baseline	19.65 ± 8.78	21.15 ± 9.39	18.61 ± 8.38	0.329
Walking step test with CSAI	16.11 ± 6.82	16.77 ± 9.29	15.69 ± 4.89	0.632
Non-motor assessment				
TMSE score at baseline	26.90 ± 2.93	27.69 ± 2.47	26.54 ± 3.08	0.198
TMSE score with CSAI	26.96 ± 2.91	27.63 ± 2.50	26.66 ± 3.07	0.214
UPDRS I: mentation, behavior, and mood section score, at baseline	10.57 ± 2.78	11.60 ± 3.04	10.09 ± 2.56	0.083
UPDRS I: mentation, behavior, and mood section score with CSAI	7.26 ± 2.50	7.53 ± 2.36	7.13 ± 2.59	0.607
NMSQ at baseline	18.63 ± 4.76	15.25 ± 6.17	20.17 ± 2.95	0.001*
• Digestive domain	5.27 ± 1.44	4.19 ± 1.91	5.77 ± 0.81	0.003*
• Urinary domain	1.61 ± 0.78	0.94 ± 0.99	1.91 ± 0.37	<0.001*
• Memory domain	2.47 ± 1.08	1.75 ± 1.44	2.80 ± 0.67	0.001*
• Hallucination/ delusions	0.37 ± 0.66	0.75 ± 0.78	0.20 ± 0.53	0.003*
• Depression/ anxiety domain	1.80 ± 0.60	1.50 ± 0.89	1.94 ± 0.34	0.015*
• Sexual function domain	1.61 ± 0.80	1.75 ± 0.68	1.54 ± 0.85	0.392
• Cardiovascular domain	1.59 ± 0.78	1.00 ± 1.03	1.86 ± 0.43	0.001*
• Sleep disorder domain	3.55 ± 1.58	2.50 ± 1.71	4.03 ± 1.27	0.005*
• Miscellaneous domain	0.35 ± 0.80	0.88 ± 1.15	0.11 ± 0.40	0.002*
NMSQ with CSAI	12.45 ± 3.62	9.56 ± 3.96	13.77 ± 2.58	0.001*
• Digestive domain	3.47 ± 1.41	2.56 ± 1.15	3.89 ± 1.32	0.001*

(*continued on next page*)

Table 1 (*continued*)

Category	Apomorphine users			*p*-value (continuing vs. discontinued users)
	All users (N = 51)	Continuing users (N = 16)	Discontinued users (N = 35)	
• Urinary domain	1.57 ± 0.78	0.88 ± 0.96	1.89 ± 0.40	<0.001*
• Memory domain	2.45 ± 1.08	1.69 ± 1.40	2.80 ± 0.67	<0.001*
• Hallucination/ delusions	0.29 ± 0.58	0.56 ± 0.73	0.17 ± 0.45	0.021*
• Depression/ anxiety domain	0.22 ± 0.46	0.25 ± 0.58	0.20 ± 0.41	1.000
• Sexual function domain	0.90 ± 0.94	0.81 ± 0.98	0.94 ± 0.94	0.630
• Cardiovascular domain	0.78 ± 0.46	0.44 ± 0.63	0.94 ± 0.24	<0.001*
• Sleep disorder domain	2.43 ± 1.06	1.56 ± 1.21	2.83 ± 00.71	<0.001*
• Miscellaneous domain	0.33 ± 0.74	0.81 ± 1.04	0.11 ± 0.40	0.003*
NMSQ delta	6.18 ± 2.84	5.69 ± 3.51	6.40 ± 2.49	0.602
• Digestive domain	1.80 ± 1.36	1.63 ± 1.50	1.89 ± 1.30	0.503
• Urinary domain	0.04 ± 0.39	0.06 ± 0.57	0.03 ± 0.29	0.798
• Memory domain	0.02 ± 0.14	0.00 ± 0.00	0.00 ± 0.00	0.139
• Hallucination/ delusions	0.08 ± 0.68	0.19 ± 0.75	0.03 ± 0.66	0.376
• Depression/ anxiety domain	1.59 ± 0.69	1.25 ± 0.93	1.74 ± 0.51	0.057
• Sexual function domain	0.71 ± 1.10	0.94 ± 1.12	1.20 ± 0.83	0.244
• Cardiovascular domain	0.80 ± 0.66	0.56 ± 1.03	0.91 ± 0.37	0.055
• Sleep disorder domain	1.12 ± 0.93	0.94 ± 1.12	1.20 ± 0.83	0.094
• Miscellaneous domain	0.02 ± 0.14	0.06 ± 0.25	0.00 ± 0.00	0.139
ADL and QOL assessment				
UPDRS II: ADL section score, on period at baseline	17.96 ± 6.86	19.07 ± 5.05	17.47 ± 7.53	0.472
UPDRS II: ADL section score, on period with CSAI	12.89 ± 5.99	13.71 ± 4.03	12.52 ± 6.72	0.463
PDQ-8 at baseline	14.86 ± 6.65	13.36 ± 6.74	15.50 ± 6.63	0.379
PDQ-8 with CSAI	10.78 ± 6.28	9.00 ± 4.79	11.53 ± 6.76	0.267
Complication of treatment assessment				
UPDRS IV: complication section score, at baseline	16.83 ± 3.11	17.33 ± 3.16	16.59 ± 3.11	0.458
UPDRS IV: complications section score with CSAI	8.87 ± 3.78	9.40 ± 3.42	8.63 ± 3.96	0.518
Follow-up periods (days)	626.20 ± 619.17	986.93 ± 645.03	467.06 ± 486.74	0.021*

Statistical analysis was performed by Mann-Whitney *U* test and Chi-square test. *A p*-value was calculated for the comparison between continue and discontinue users. SAI; subcutaneous apomorphine infusion, HY; Hoehn and Yahr stage, UPDRS; the unified Parkinson's disease rating scale, LED; levodopa equivalent daily dosage, NMSQ; non-motor symptoms questionnaire, PDQ-8; Parkinson's disease questionnaire- 8 items, MMSE; mini mental state examination, delta; represent the minus score between baseline and with CSAI, *; statistical significance with *p*-value <0.05.

increase in the walking step test were found ($p < 0.05$, each). For non-motor outcomes, as shown in Fig. 1B, a reduction in both UPDRS I and NMSQ (in total scores and sub-scores (digestive domain, depression domain, sexual domain, cardiovascular domain, and sleep domain) were found ($p < 0.05$, each). For ADL and QOL assessment, as shown in Fig. 1C, significant reductions in UPDRS II and PDQ-8 were found ($p < 0.05$, each). For complication of treatment outcomes, a significant reduction in UPDRS IV was found ($p < 0.05$). The most common complication of CSAI during titration was subcutaneous nodules (31 patients, 60.8%), followed by device complexity (16 patients, 31.4%), dyskinesia (16 patients, 31.4%), unmet satisfaction (16 patients, 31.4%), nausea (14 patients, 27.5%), hallucinations (12 patients, 23.5%), hypotension (12 patients, 23.5%), compulsive disorders (8 patients, 15.7%), and severe abdominal bruising due to concomitant use of anticoagulation (1 patient, 1.9%).

3.3. Comparison of clinical parameters between continued and discontinued users

Comparisons of clinical parameters recorded at the time of CSAI titration between continued and discontinued users are shown in Table 1. The presence of a full-time caregiver was significantly higher in continued users, compared to discontinued users, with similar results observed for other parameters, including greater daily off hours reduction, lower UPDRS motor section score, better performance in the finger tapping test on the most affected side, lower NMSQ score at baseline (in total score and sub-scores), and lower NMSQ score at the time of CSAI titration (in total score and sub-scores) ($p < 0.05$, each). However, the scores for the hallucination domain at baseline and during CSAI titration were significantly higher in continued users compared to discontinued users ($p < 0.05$). NMSQ scores between baseline and during CSAI titration (delta NMSQ score) were no different between continued and discontinued users in both total NMSQ score and sub-scores ($p > 0.05$, each). In addition, a follow-up period for drug use was longer in continued users, compared to discontinued users ($p < 0.05$).

3.4. Calculation of ROC and survival analysis for determining discontinuation of CSAI

After completing CSAI titration, patients who continued CSAI usage were recruited to the long-term cohort study. So far, the shortest duration of CSAI use was 24 days, while the longest duration of CSAI used was 2363 days with a mean duration of CSAI use of 626.2 days (SD 619.17). Bolus or intermittent injections together with the infusion method were reported in 43 (78.2%) patients. 35 patients (68.6%) discontinued CSAI for various reasons. ROC analysis was performed to calculate the cut-off points of variables at the time of CSAI titration that determine discontinuation of CSAI in the long-term study, as well as to estimate sensitivity and specificity of the cut-off point. For off hours reduction at the time of CSAI titration, as shown in Fig. 1D, ROC analysis revealed area under the curve (AUC) of 0.731 (SD 0.074) ($p = 0.009$), suggesting that reduction in daily off hours at the time of CSAI titration can distinguish between patients who will continue and those who will discontinue CSAI therapy over the long-term, with a cut-off point of 3.5 h or more (sensitivity, 75%; specificity, 57.1%). For NMSQ scores at the time of CSAI titration, as shown in Fig. 1E, ROC analysis revealed AUC of 0.796 (SD 0.076) ($p = 0.001$), suggesting that NMSQ scores at the time of CSAI titration can distinguish between patients who will continue and those who will discontinue CSAI therapy over the long-term, with a cut-off score of 9.5 points or more (sensitivity, 94.3%; specificity, 50.0%). Table S2 shows the relative risk results of the univariate analysis for the selected variables at the time of CSAI titration. Discontinuation of CSAI was associated with the following factors: an absence of full-time caregivers; achieving a daily off-time reduction at the time of CSAI titration <3.5 h; and NMSQ scores at the time of CSAI titration ≥9.5 points. Fig. 1F shows the Kaplan-Meier survival curves. Overall comparison

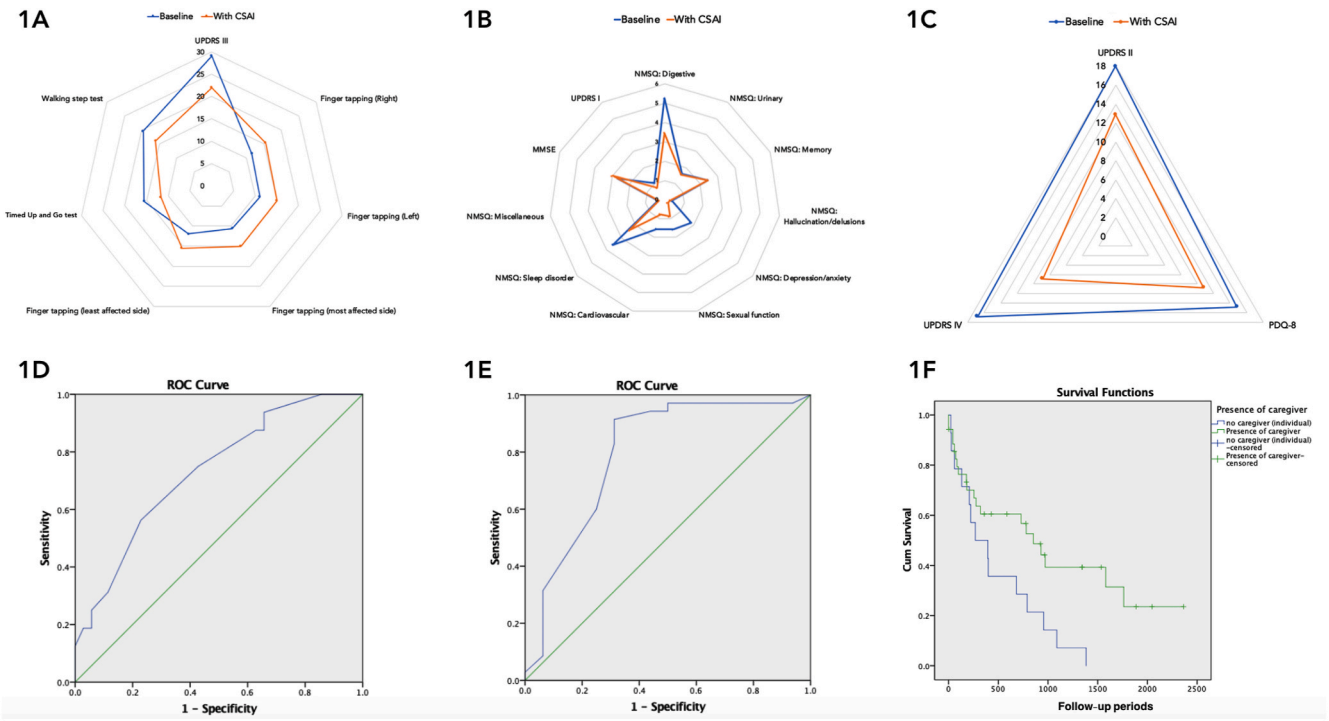

Fig. 1. A represents the comparison of motor outcomes between baseline and with CSAI.
Fig. 1B represents the comparison of non-motor outcomes between baseline and with CSAI. Fig. 1C represents the comparison of ADL, QOL and complication of treatment between baseline and with CSAI. Fig. 1D represents the ROC analysis for the cutoff scores of daily off hour reduction at the time of CSAI titration that might determine discontinuation. Fig. 1E represents the ROC analysis for the cutoff scores of NMS scores at the time of CSAI titration that might determine discontinuation. Fig. 1F shows Kaplan Meyer plot for determine the effect of presence of caregiver and continuation of CSAI.

with Log Rank methods shows a highly significant difference in the continuation of CSAI was found between patients who had a full-time caregiver and those who had no caregiver ($X^2 = 5.399$, $p = 0.020$). The mean survival time for patients with a full-time caregiver was 1052.93 days (SD 172.66) whereas the mean survival time for those without was 475.00 days (SD 116.17).

4. Discussion

CSAI remains a proven add-on therapy for treating motor complications in patients with PD with good efficacy and tolerability found in both clinical studies and in clinical practice [1,6,10]. Compared to oral medications, CSAI is a relatively new treatment in Thailand, with increasing complexity throughout the course of treatment [6]. Recently, a study was published to assess the efficacy and outcomes of CSAI in Indian patients, providing retrospective insight on short-term efficacy of CSAI amongst an Asian population [11]. This current study adds weight the growing evidence by including a representative Asian cohort within which factors affecting CSAI were investigated in motor, non-motor, ADL, and QOL outcomes, as well as providing a platform for data collection on patient demographics and clinical outcomes and comprehensive survival analysis to determine the discontinuation of treatment.

Similar to previous studies, this study confirmed the beneficial effect of CSAI on the management of motor complications [1,3,12]. Identical to previous study reported the potential discontinuation rate of this treatment, of the 51 patients recruited, 35 (68.6%) discontinued before the study conclusion [7]. We identified three main factors predicting the discontinuation of CSAI in a long-term including; 1) achieving a daily off hour reduction at the time of CSAI titration <3.5 h; 2) NMSQ scores at the time of CSAI titration ≥9.5 points; and 3) an absence of full-time caregivers. To be more explicit, although both continued and discontinued users showed improvement in all clinical outcomes during CSAI titration, the degree of improvements with CSAI amongst continued users was significantly higher than discontinued users in parameters including UPDRS motor section score, daily off hours reduction, and finger tapping test on the most affected side (all, $p < 0.05$). Therefore, patients' expectations may play a significant role in any treatment continuation, with patients more likely to discontinue treatment if benefits do not reach their expectations [2,7]. Consistently with our results, achieving a daily off hour reduction at the time of CSAI titration less than 3.5 h is unsatisfactory to patients and leads to discontinuation of CSAI in the long-term (with a relative risk of 1.500). Similar to a previous study, our study also showed significant improvements with CSAI in a variety of areas, including motor outcomes (UPDRS 3), non-motor outcomes (NMSQ), QOL outcomes (PDQ-8), and complication of treatment outcomes (UPDRS IV) [13]. In addition, although no change in cognitive score was noted in this study, we found that non-motor outcomes at the time of CSAI titration played a significant role in discontinuation of the treatment. At the time of CSAI titration, continued users reported a lower severity of NMSQ compared to discontinued users in the following domains; digestive, urinary, memory, cardiovascular, sleep, and miscellaneous. The miscellaneous domain comprised of items relevant to pain, change in weight, leg swelling, excessive sweating, and double vision [9]. Our findings are consistent with the previous publication that reported improvement of specific NMS with CSAI such as hyperhidrosis, nocturia, urgency of micturition, and fatigue [13]. After treating with CSAI, persisting NMS including orthostatic hypotension, visual hallucinations, excessive daytime sleepiness, and nausea were associated with discontinuation in a long-term follow-up [14]. Similarly, in this study, a NMSQ score at the time of CSAI titration of ≥9.5 points was important for discontinuation of CSAI in the long-term (with a relative risk of 4.024). In addition, patients who had no full-time caregiver had a greater tendency to discontinue CSAI than those with a full-time caregiver, thus representing an important factor for long-term engagement of patients in CSAI (with a relative risk of 1.762). A Kaplan-Meier plot confirms this finding that the

same cumulative percentage of patients who had full-time caregivers had a longer continuation of CSAI. Our results should help physicians to better understand a patient's drug response, identify which patients are likely to discontinue CSAI over the long-term, and indicates how neurologists can support them to allow continuation of this therapy. Involvement of a multidisciplinary care team, comprised of movement disorder specialists, specialist PD nurses, PD nurse assistants, and apomorphine patient advocates, in this treatment may be key for supporting both patient and caregiver engagement, maximising adherence, and play an essential role in patient education, which is vital for the long-term success of CSAI [8].

Though, we report here on the first cohort of Thai PD patients, this study does have limitations. Our centre is a tertiary-care centre with the most CSAI users in Thailand (Fig. S1), but since the participants were solely from our centre, they may not fully represent the characteristics of patients with advanced PD who have undergone CSAI in Thailand. To counter this bias, we are in the process of recruiting additional centres performing CSAI in Thailand to expand this registry.

In conclusion, the results from this registry provide support for the efficacy and safety of CSAI for patients of Asian ethnicity with advanced PD. An absence of a full-time caregiver, daily off hours reduction at the time of CSAI titration of $<$3.5 h and NMSQ scores at the time of CSAI titration $\geq$9.5 points were potential factors that might determine the discontinuation of CSAI treatment.

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Author contributions

Concept or design of the work, O.P., R.C., T.V.L., and R.B.; acquisition, analysis, and interpretation of data, O.P., C.A., and A.P.; first drafting the manuscript, O.P. and R.B; critique and revising the manuscript, O.P., R.C., T.V.L., and R.B. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.09.022.

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