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Tolerability of perampanel: a retrospective study at the department of psychiatry

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ABSTRACT

Purpose

We aimed to identify factors that contribute to the discontinuation of perampanel.

Methods

We retrospectively analyzed patients with epilepsy at the Department of Psychiatry, Hokkaido University Hospital. We evaluated the factors contributing to perampanel discontinuation as primary outcomes using Cox proportional hazards regression. Then, we explored the components contributing to the primary outcomes using logistic regression analysis.

Results

A total of 118 patients were included, 44.9% of whom discontinued participation, 22.0% had intellectual disability, and 23.7% had a psychiatric disorder other than intellectual disability. Adverse effects occurred in 65% of the patients, 23.7% had psychiatric adverse effects (PAE), and 49.2% had common adverse effects (CAE).The effect of PER to suppress seizures was confirmed in 65.3% of them. Discontinuation was influenced by non-response (Hazard Ratio (HR) 6.83, 95% Confidence Interval (CI) 3.48–13.4), the occurrence of PAE (HR 3.75, 95% CI 1.88–7.47), CAE (HR 1.99, 95% CI 1.09–3.63), and comorbid psychiatric disorders (HR 2.20, 95% CI 1.13–4.28). Moreover, comorbid intellectual disability correlated with a low risk of PAE (OR 0.18, 95% CI 0.04–0.87).

Conclusion

The discontinuation of perampanel is influenced by poor efficacy and the occurrence of common/psychiatric adverse effects. The discontinuation of perampanel is influenced by poor efficacy and the occurrence of common/psychiatric adverse effects. Consideration of factors contributing to perampanel discontinuation may assist in determining the indication for perampanel treatment.

KEYWORDS

perampanel, psychiatric adverse effects, psychiatric comorbidity, Intellectual disability, anti-seizure medication

ABBREVIATIONS

PER, perampanel; PAE, psychiatric adverse effects; CAE, common adverse effect; ASM, anti seizure medications; HR, hazard ratio; OR, odds ratio; CI, Confidence interval; SD, standard deviation

1. INTRODUCTION

Discontinuing anti-seizure medications (ASM) is a common clinical challenge [1]. Perampanel (PER) is a broad-spectrum ASM that is effective as monotherapy and combined with other agents. Adverse effects of PER commonly involve the central nervous system such as dizziness, sleepiness, and headache [2]. However, psychiatric adverse effects such as irritability and depression occur in 5–10% of patients [1,3]. Particularly, cognitive decline, headache, fatigue, and weight gain can influence the patients' decision to discontinue the medication [4]. However, the risk factors leading to PER discontinuation are not well understood. Therefore, this study aimed to evaluate the factors that contribute to the discontinuation of PER.

2. MATERIAL AND METHODS

This was a single-center retrospective observational study conducted at Department of Psychiatry, Hokkaido University Hospital that is one of the Epilepsy Centers in Japan. The study was approved by the ethics committee of the affiliated institution (023-0021). We first detected patients who had visited the Epilepsy Outpatient Clinic in our department between July 1, 2021, and June 30, 2022. We included both patients seen as return visits and those seen as initial visits. Then, medication history including prior to 2021 was examined and patients who were newly prescribed PER at our outpatient clinic were included. All patients were examined regularly by doctors who were both certified epileptologists and certified psychiatrists (TH and YN). Epilepsy diagnoses were based on ILAE 2017, and psychiatric evaluation was based on Diagnostic and Statistical Manual of mental disorders (DSM-5) [5]. Medical records were used to collect data on the patients' age, sex, epilepsy classification,

comorbidities, adverse effects, number of concomitant ASM (including whether the ASM inducing cytochrome P450 3A4 (CYP3A4)), PER dose, whether PER treatment was discontinued, and the duration for which PER was administered. Comorbidities were defined as psychiatric disorders listed in the DSM-5. Among the adverse effects, irritability, depression, visual hallucinations, auditory hallucinations, and emotional instability were defined as psychiatric adverse effects (PAE). Other symptoms, such as lightheadedness, dizziness, headache, and nausea, were described as common adverse effects (CAE). The “maximum dose” was defined as the maximum dose prescribed to an individual. Effectiveness was defined as "reduced number of seizures" in the medical record and was divided into "response" and "non-response". "Non-response" included exacerbation and unknown.

The primary outcome was the discontinuation of PER treatment. Time-to-event was defined as the time interval from the date of initiation of PER treatment to the date of treatment discontinuation or the end of the last follow-up (36 months). We used a Cox proportional hazards regression model with the dependent variable being the discontinuation of PER treatment, and the independent variables being age, sex, epilepsy classification, comorbidity of intellectual disability, comorbidity of mental illness, efficacy, CAE, PAE, dose of PER, and the number of concomitant ASM. Data were presented as hazard ratios (HR) and 95% confidence intervals (CI). The secondary outcome was the occurrence of PAE, CAE, and the presence or absence of effects. Logistic regression analysis was used to explore the factors associated with the secondary outcomes. For this analysis, the dependent variables were the secondary outcome variables, and the independent variables were age, sex, epilepsy classification, comorbidity of intellectual disability, comorbidity of mental illness, dose of PER, the number of concomitant ASM, and presence or absence of concomitant use of

CYP3A4-inducing drugs. Data were presented as odds ratio (OR) and 95% CI. All analysis were done using R statistics 4.0.2. The significance level was set at $p<0.05$.

3. RESULTS

Of the 994 initially screened patients, 118 (11.9%) received PER treatment. Table 1 shows the characteristics of patients prescribed PER (showed as overall, discontinued, and continued groups). Seventy patients (59.3%) were women, 100 (84.7%) had focal epilepsy, 26 (22.0%) had comorbid intellectual disability, 58 (49.2%) had CAE, and 28 (23.7%) had PAE.

Table 1. Characteristics of the patients who were on perampanel treatment.

		discontinued 53 (44.9%)	continued 65 (55.1%)	overall 118 (100%)
mean age ± SD		47.1±12.1	42.4±9.9	44.5±11.2
female, n (%)		35 (66.0%)	35 (53.8%)	70 (59.3%)
epilepsy types				
	focal epilepsy	50 (94.3%)	50 (76.9%)	100 (84.7%)
	generalized epilepsy	1 (1.9%)	7 (10.8%)	8 (6.7%)
	other types	0 (0.0%)	3 (4.6%)	3 (2.5%)
comorbidity				
	intellectual disability	6 (11.3%)	20 (30.8%)	26 (22.0%)
	psychiatric comorbidity (excluding intellectual disability)	16 (30.2%)	12 (18.5%)	28 (23.7%)
dose of PER (mg)		4.35±3.17	4.95±2.93	4.68±3.05
response		19 (35.8%)	58 (89.2%)	77 (65.3%)
non-response		34 (64.2%)	7 (10.8%)	41 (34.7%)
non-adverse effects		8 (15.1%)	33 (50.8%)	41 (34.7%)
CAE		30 (56.6%)	28 (43.1%)	58 (49.2%)
PAE		23 (43.4%)	5 (7.7%)	28 (23.7%)
mean number concomitant ASMs		2.2±0.94	2.4±0.99	2.3±0.97

Abbreviations: SD, standard deviation; CAE, common adverse effects; PAE, psychiatric adverse effects; PER

Of the 118 patients, 53 (44.9%) discontinued PER. Comorbidities were present in 22 (41.5%) patients in the discontinued group, and 29 (44.6%) in the continued group. Adverse effects occurred in 45 (84.9%) patients in the discontinued group, and 32 (49.2%) in the continued group. The mean daily dose was 4.3±2.5 mg for women and 5.5±3.7 mg for men.

Figure 1A shows the survival curve for all subjects, and Figure 1B–1D shows the survival curves divided into two groups based on the presence/absence of PAE, CAE, and the effect of PER.

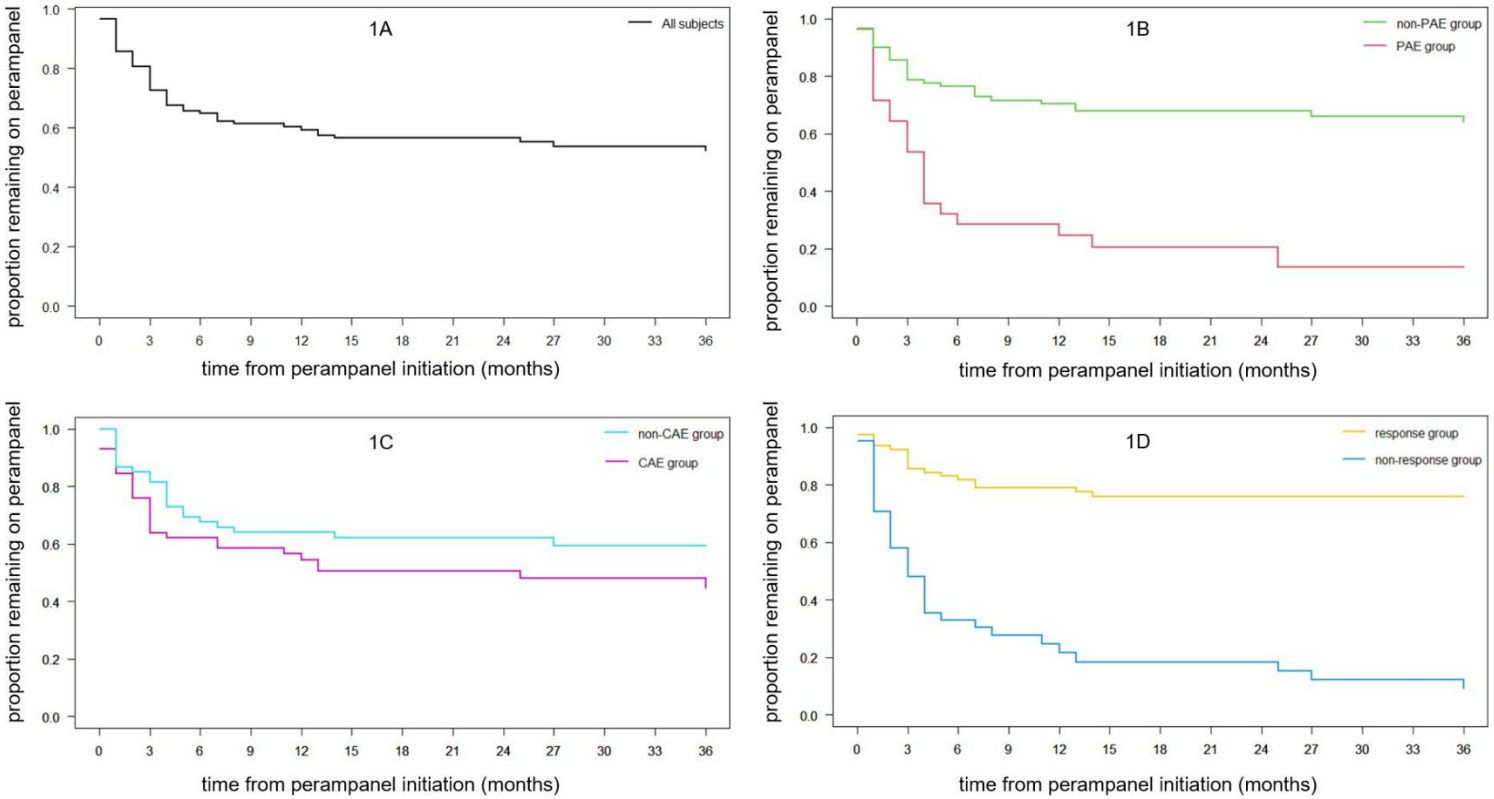

Figure 1. Survival curves for each group treated with PER: 1A for all subjects (n=118), 1B for PAE (PAE group n=28, non-PAE group n=90), 1C for CAE (CAE group n=58, non-CAE group n=60), 1D indicates presence or absence of effect (response group n=77, non-response group n=41).

During the 36-month follow-up period, 45.0% of the patients discontinued PER treatment. Of these, 82.1% were in the PAE group, 33.3% in the non-PAE group, 51.7% in the CAE

group, 38.3% in the non-CAE group, 24.7% in the response group and 82.9% in the non-response group.

Table 2 shows the Cox analysis with discontinuation of PER treatment as the outcome. Non-response (HR 6.70, 95% CI 3.42–13.1), occurrence of PAE (HR 3.68, 95% CI 1.89–7.16), occurrence of CAE (HR 1.90, 95% CI 1.06–3.41), and psychiatric comorbidity (HR 2.35, 95% CI 1.21–4.59) were significantly associated with discontinuation of PER treatment.

Table 2. Cox analysis with discontinuation of PER treatment as the outcome.

	Reference	HR	95%CI
age	NA	1.01	0.98–1.04
female	(vs. male)	0.67	0.34–1.30
generalized epilepsy	(vs. focal epilepsy)	0.55	0.07–4.23
other type	(vs. focal epilepsy)	0.53	0.12–2.50
intellectual disability	(vs. non–intellectual disability)	0.67	0.28–1.62
psychiatric comorbidity	(vs. non–psychiatric comorbidity)	*2.35	1.21–4.59
CYP3A4 Inducer	(vs. non-inducer)	1.28	0.70–1.15
non-response	(vs. response)	**6.70	3.42–13.1
CAE	(vs. non-CAE)	*1.90	1.06–3.41
PAE	(vs. non-PAE)	**3.68	1.89–7.16
dose of PER	NA	1.04	0.94–1.15
number of concomitant ASM	NA	0.86	0.62–1.20

Abbreviations: ASM, anti-seizure medication; CAE, common adverse effects; CYP3A4, cytochrome P450 3A4; HR, hazard ratio; PAE, psychiatric adverse effects; NA, not applicable; *, $p<0.05$; **, $p<0.001$.

Logistic regression analysis was performed to explore the variables associated with the three factors related to PER treatment (non-response, occurrence of PAE, and occurrence of CAE). The results are presented in Table 3. Women and non-response to treatment were significantly associated (OR 2.71, 95% CI 1.13–6.53), intellectual disability and the occurrence of PAE were significantly associated (OR 0.18, 95% CI 0.04–0.87), the occurrence of CAE, although more common among women, was not significantly associated with PER (OR 2.10, 95%CI 0.91–4.45).

Table 3. Variables associated with non-response, PAE, and CAE after PER treatment

	PAE		CAE		Non-response	
	OR	95%CI	OR	95%CI	OR	95%CI
Age	1.00	0.95–1.04	0.99	0.96–1.03	1.04	1.00–1.08
female	2.18	0.81–5.86	2.10	0.91–4.45	*2.74	1.10–6.83
generalized epilepsy	0.94	0.16–5.61	0.60	0.12–2.85	0.27	0.03–2.51
other type	0.00	inf	0.62	0.16–2.51	1.70	0.40–7.12
intellectual disability	*0.19	0.04–0.89	0.98	0.39–2.48	0.44	0.15–1.30
psychiatric comorbidity	1.10	0.37–3.30	0.84	0.33–2.14	0.38	0.13–1.12
CYP3A4 inducer	1.05	0.35–3.10	1.76	0.72–4.34	1.36	0.52–3.53
dose of PER	0.91	0.76–1.08	0.94	0.83–1.08	0.89	0.76–1.04
number of concomitant ASM	1.28	0.80–2.06	1.03	0.70–1.53	1.41	0.90–2.21

Abbreviations: ASM, anti-seizure medication; CAE, common adverse effects; CYP3A4, cytochrome P450 3A4; OR, odds ratio; PAE, psychiatric adverse effects; *, $p<0.05$.

4. DISCUSSION

In this study, we investigated the factors that influence PER discontinuation. Non-response, the occurrence of PAE, the occurrence of CAE, and psychiatric comorbidities were the main obstacles to PER treatment. Furthermore, women were less likely to respond to PER treatment than men were, and comorbid intellectual disability was associated with a low incidence of PAE.

This study reported that the overall discontinuation rate of PER during a follow-up period was 44.9%, which was similar to that reported previously [6].

Non-responsiveness to the treatment was the largest contributor to discontinuation of PER treatment, and in women, the efficacy of PER treatment was significantly poor. Previous reports have shown that PER was more effective in women [7;8], or that no sex difference existed in the efficacy of PER treatment [9;10]. In our data, the difference in findings could be due to the fact that women were administered relatively lower doses (4.27 ± 2.54 mg) than those administered to the men (5.17 ± 3.5 mg) although the difference was not significant (Table S1)

The rate of PAE was associated with discontinued PER treatment with a HR of 3.68. The rate of PAE reported in our study was 24.2%, which was almost double that reported in a previously published in a systematic review (12.3%) [11]. It was possible that in our clinical setting, the adverse effects related to psychiatric symptoms were more likely to be captured since psychiatrists examined the patients. Also, as the patients or their companions were well-informed about the potential adverse effects in advance might have contributed to the high rate. Logistic regression analysis revealed that PAE was inversely associated with intellectual disability. Previous studies have shown that intellectual disability increased the risk of PAE in populations including children [12], and that aggression was more common in adolescents

[13]. However, our study was conducted in adults who visited the department of psychiatry. Further, we fully explain the risks of PAE associated with PER to the patient and family when prescribing PER, and only if the patient and family actively want to use the drug, we prescribe it. We start the drug at a low dose and increase the dose at a slower pace. Furthermore, it was possible that some or most of the patients did not have an irritable personality, or the family members, knowing the side effects beforehand, were better equipped to handle those situations, and this could have influenced the results seen in our study.

CAE occurred at a rate of 49.2% and was associated with discontinued PER treatment with a HR of 1.90. Logistic regression analysis showed no significant associations with the studied factors, but women tended to have a higher rate of CAE. This finding was consistent with previous reports [14]. In the present study, only factors that could predict each endpoint at the start of PER treatment were entered as independent variables. Therefore, the PER dose, which was constant at the beginning of the treatment and changes throughout the treatment, was not included as a time-dependent variable. However, since the dose of PER may affect many endpoints, a time-dependent validation (time-dependent COX analysis) was considered necessary but could not be performed in this study.

Psychiatric comorbidity was significantly associated with discontinuation of PER with a HR of 2.35. Previous studies have shown that PAE was more likely to lead to discontinued PER treatment [12], and that psychiatric disorders could trigger PAE [15]. However, our study is the first to show that comorbid psychiatric disorders were more likely to lead to discontinuation of PER. When prescribing PER to patients with psychiatric comorbidities, it is advisable to be aware of the possibility of discontinuation afterward.

5. LIMITATION

This manuscript presented a retrospective analysis derived from medical records, which was subject to several limitations. Firstly, the study may not accurately delineate the effects and adverse effects of pharmaceuticals both before and after the PER start due to the absence of structured interviews or rating scales and failed to consider the combination of drugs administered. Additionally, there exists potential selection bias concerning prescriptions of PER. The lack of pediatric cases from the study necessitates caution in generalizing the findings. Moreover, the variability in PER dose and the number of ASM could influence endpoints, rendering time-dependent validation desirable [16]. Unfortunately, such validation was unfeasible due to the lack of temporal data in our dataset. Our study was further constrained by a small sample size, which did not satisfy the criterion of ten events per variable (EPV) [17], although it is acknowledged that under certain circumstances, coverage and bias remain acceptable with an EPV below ten [18]. Nevertheless, the confidence interval for the observed associations was narrow, suggesting that the point estimates provided were reliable. Future investigations could provide more robust evidence through the expansion of sample size, execution of prospective studies, or implementation of multicenter studies with adjustments for inter-institutional bias.

6. CONCLUSIONS

The discontinuation of PER treatment is influenced by poor efficacy and the occurrence of common/psychiatric adverse effects. Consideration of factors contributing to perampanel discontinuation may assist in determining the indication for perampanel treatment.

REFERENCES

1. Brodie MJ, et al. Epilepsy, antiepileptic drugs, and aggression: an evidence-based review. Pharmacological reviews. 2016;68(3):563–602.
2. Rugg-Gunn F, et al. Adverse effects and safety profile of perampanel: a review of pooled data. Epilepsia. 2014;55:13–15.
3. Gil-Nagel A, et al. A retrospective, multicentre study of perampanel given as monotherapy in routine clinical care in people with epilepsy. Seizure. 2018;54:61–66.
4. Singh K, et al. Safety and efficacy of perampanel in children and adults with various epilepsy syndromes: a single-center postmarketing study. Epilepsy & Behavior. 2016;61:41–45.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., Washington, DC, 2013.
6. Villanueva V, Garcés M, López-González FJ, et al. Safety, efficacy and outcome-related factors of perampanel over 12 months in a real-world setting: The FYDATA study. Epilepsy Res. 2016;126:201–210. doi:10.1016/j.eplepsyres.2016.08.001
7. Vazquez Blanca, et al. "Perampanel efficacy and safety by gender: subanalysis of phase III randomized clinical studies in subjects with partial seizures." Epilepsia 56.7 (2015): e90–e94.
8. Dekker MJHJ, et al. "Sex proportionality in pre-clinical and clinical trials: an evaluation of 22 marketing authorization application dossiers submitted to the European medicines Agency." Frontiers in medicine 8 (2021): 133.
9. Zhang Wei-Ran, et al. "Efficacy of perampanel as an adjunctive therapy in pediatric focal epilepsy." World Journal of Pediatrics (2023): 1–4.

10. Wehner T, Mannan S, Turaga S, et al. Retention of perampanel in adults with pharmacoresistant epilepsy at a single tertiary care center. Epilepsy Behav. 2017;73:106–110. doi:10.1016/j.yebeh.2017.04.006
11. Steinhoff BJ, Klein P, Klitgaard H, et al. Behavioral adverse events with brivaracetam, levetiracetam, perampanel, and topiramate: A systematic review. Epilepsy Behav. 2021;118:107939.
12. Yamamoto Y, et al. "Risk factors for psychiatric adverse effects associated with perampanel therapy." Epilepsy & Behavior 124 (2021): 108356.
13. Hansen Cerine C., et al. "Mechanisms underlying aggressive behavior induced by antiepileptic drugs: focus on topiramate, levetiracetam, and perampanel." Behavioural neurology 2018 (2018).
14. Toledano DR, et al. "Effectiveness and safety of perampanel monotherapy for focal and generalized tonic-clonic seizures: Experience from a national multicenter registry." Epilepsia 61.6 (2020): 1109–1119.
15. Hasegawa N and Tohyama J. "Differences in levetiracetam and perampanel treatment-related irritability in patients with epilepsy." Epilepsy & Behavior 116 (2021): 107644.
16. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med. 2018;6(7):121-121. doi:10.21037/atm.2018.02.12
17. Peduzzi P, Concato J, Kemper E, Holford TR, and Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373–1379.
18. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and cox regression. Am J Epidemiol. 2007;165(6):710–718. doi:10.1093/aje/kwk052