

Title: An evaluation of the effectiveness of perampanel in people with epilepsy who have previously undergone resective surgery and/or implantation of a vagal nerve stimulator

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Some minor changes in purple, if you are happy just accept these – no need to highlight to editors/reviewers

Abstract

About 30% of people with epilepsy (PWE) are drug-resistant. Those with focal seizures may be suitable for epilepsy surgery. Those not amenable to resective surgery can be considered for vagus nerve stimulation (VNS). However, after operative procedures, around 50% of patients continue to experience seizures.

A multi-center retrospective study assessing perampanel **effectiveness** and tolerability for PWE who have undergone surgical resection and/or VNS implantation was performed. The primary outcome was $\geq 50\%$ reduction in seizure frequency while secondary outcomes included side effects (SEs), dose-related effectiveness and toxicity. The median perampanel dose was 6mg. Only one PWE became seizure free. A $\geq 50\%$ decrease in seizure frequency was observed in 52.8% of the post-resection group and 16.9% of the VNS group ($p < 0.001$), while SEs were seen in 44.8% and 41.1% respectively. Perampanel doses greater than 8mg led to better response in both groups, especially in the post-VNS cohort. SEs were not dose-related and the safety profile was similar to previous observational studies.

Perampanel can be beneficial in these two super-refractory epilepsy groups, particularly in PWE with seizures after surgical resection. Doses of more than 8mg appear to be well tolerated and may be more effective than lower doses in PWE after surgical interventions.

Keywords:

Anti-seizure medication; epilepsy surgery; pharmacoresistant epilepsy; seizures; VNS

Abbreviations

ASDs, antiseizure drugs; BTCS, bilateral tonic-clonic seizures; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; PWE, people with epilepsy; SE, side effects; TLE, temporal lobe epilepsy; VNS, vagus nerve stimulation

Disclosures

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1. Introduction

Around 30% of people with epilepsy (PWE) remain refractory to currently available medical treatment[1]. Individuals with pharmacoresistant focal epilepsy may be suitable for surgical resection of the epileptogenic zone. However, more than 50% of PWE undergoing epilepsy surgery can experience seizure recurrence within 10 years post-resection[1]. PWE with drug-resistant focal or generalized epilepsy not amenable to surgery can be considered for vagus nerve stimulation (VNS)[2]. VNS implantation can reduce the frequency and severity of seizures[2], but is not necessarily curative. Therefore, after both resective surgery and VNS implantation, a considerable number of PWE will continue to experience seizures. By definition, this cohort will have trialled multiple agents prior to operative intervention and represent a group with severe pharmacoresistant epilepsy, often with multiple co-morbidities.

During the last 30 years, several “second generation” ASDs have been developed. The expectation for significantly improved outcomes in drug-resistant epilepsy has not necessarily been fulfilled and only a modest impact on drug-resistance has been observed[3]. However, the newer drugs have found their place in the treatment of epilepsy providing alternative options and, generally, a better safety profile[3]. The identification of PWE subgroups that could benefit from specific ASDs is of unparalleled importance in order to provide optimal treatment with higher chances for improvement in seizure control and reduced side effects.

Perampanel (PER) was licensed in the UK in 2013 for pharmacoresistant epilepsy. There are a number of PWE who have undergone resection or VNS insertion without exposure to PER. These PWE may therefore be prescribed PER if seizures persist or recur. Data regarding the efficacy and tolerability of PER in the post-surgery/VNS group with seizures are scarce. To help address this, the efficacy of PER in PWE who had undergone resection or/and VNS placement for epilepsy was assessed. Determining the efficacy of PER in this patient population will help to establish whether PER may be a drug of choice for this vulnerable group:-

2. Methods

A multi-centre retrospective clinical study with data from epilepsy centers across the UK was performed. Inclusion criteria were: age ≥ 18 , prescription of PER following resection or/and VNS implantation for treatment of epilepsy, confirmed seizures after the surgical intervention, medical records available for 6 months prior to and post-commencement of PER (including seizure diaries and seizure types) and no other changes in their antiseizure medications during this period. Individuals who had trialled PER prior to operative intervention or for whom seizure diaries were incomplete in the 6 months prior to and after commencement of PER were excluded. The primary outcome was seizure frequency reduction $\geq 50\%$ from baseline. Secondary outcomes included evaluation of side effects (SE) profile and seizure freedom. Dose-related effects of PER on outcomes and SEs were also explored.

Continuous variables were compared with the Student's t-test and categorical variables with the Chi-square, Fisher or Barnard's exact tests. For seizure frequency comparisons, data were grouped into increased seizure frequency; no change in seizure frequency; $< 50\%$ decrease; $\geq 50\%$ decrease in seizure frequency, and seizure freedom. The $< 50\%$ decrease and no change groups were then combined and compared against the $\geq 50\%$ decrease in seizure frequency groups. The effect of PER dose on seizure frequency was assessed by further analysis of these categories according to the maximal dose of PER. Statistical analysis was performed with Microsoft® Office Excel (Version 1902) and GraphPad® Prism (Version 8.1.0). Ethical approval was provided by Oxford University Hospitals NHS Foundation Trust (REF: 11349).

3. Results

A total of 113 suitable patients met the inclusion criteria (post VNS = 77, post-resection = 36). Six people within the cohort had undergone VNS implantation and resection. Of these 2 had a significant reduction in seizures with PER, but this group was too small in number for reliable statistical analysis.

The remaining post-VNS and post-resection groups were balanced for sex, mean age at review of notes, age at seizure onset and duration of epilepsy. The most common seizure types for both groups were, in descending order: focal aware seizures (FAS), bilateral tonic clonic seizures (BTCS) and focal impaired awareness seizures, (FIAS) (Table 1A). The median time from VNS implantation to PER initiation was 80 months (mean = 77 months). For surgical resection the median interval from operation to starting PER was 140 months (mean = 172 months; $p < 0.001$).

The median PER dose in each group was 6mg (mean VNS: 6.8 [SD ± 3.3]; post-resection: 7.0 [SD ± 3.3]). The additional benefit from a dose of 12mg compared to an 8mg dose was not entirely clear in the clinical trials or some pooled analysis [4-6] and responses are seen in doses ≤ 6 mg in some observational studies [7-9]. Therefore, using the mean and median doses of our cohort and these data, the cut-off for comparing low versus high-doses of PER was chosen as 8mg. There was a trend in VNS patients having PER withdrawn after 6 months more frequently than those in the post-surgical-resection group, however this was not significant (55.8% vs 44.4%, respectively, $p = 0.18$). The most frequent cause of stopping PER after 6 months in both groups was side effects (VNS 53.5%, post-resection 81.3%).

Across the entire cohort, only one patient reported seizure freedom. After treatment with PER, 52.8% of the post-resection group demonstrated a $\geq 50\%$ decrease in seizure frequency compared with 16.9% in the VNS group ($p < 0.001$; Table 1B). In the post-resection group, 61.3% demonstrated $\geq 50\%$ seizure frequency reduction (38.7% showed $< 50\%$ reduction or no seizure frequency change). In the post-VNS cohort, 20.6% demonstrated a $\geq 50\%$ reduction (79.4% had $< 50\%$ reduction in seizures; $p < 0.01$) (Table 1C).

Within the VNS group, PER doses < 8 mg led to $\geq 50\%$ seizure frequency reduction in 9.38% of cases, whereas 29.6% of cases in the ≥ 8 mg group experienced $\geq 50\%$ reduction in seizure frequency ($p < 0.01$). For the post-resection patients, PER doses < 8 mg associated with $\geq 50\%$

seizure reduction in 40% of cases; while with doses $\geq 8\text{mg}$, 55.6% of cases had $\geq 50\%$ reduction in seizure frequency (Table 1D). The frequency of side effects was not dose-dependent ($p = 0.1$).

PWE taking concurrent enzyme inducers (EI) (Phenobarbital, Phenytoin, Primidone, Carbamazepine) or sodium valproate (SV) appeared to have better response with $\geq 50\%$ responder rate at 69.2% and 91.7% respectively (when EI vs SV, $p=0.16$), (Table 1F). Comparing people taking an EI, the difference between VNS and post-resection groups 50% responders were 58.82% in the post-resection group and 17.14% in VNS group ($p<0.01$), (numbers too small to allow comparison for sodium valproate).

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4. Discussion

Our results show that PER might have a positive impact in seizure control for PWE following resective surgery or/and VNS implantation. Initiation of PER following an unsuccessful resective surgery could lead to a 50% reduction in seizure frequency in about half the patients without adding a significant burden of SE even in doses $\geq 8\text{mg}$. Therefore PER could join a number of 2nd generation ASDs in the armamentarium in these super-refractory groups.

Given that additional ASDs are more expensive than older generic versions, a tailored approach allowing specific PWE to trial certain novel ASDs earlier would also have economic benefits. Observational studies exploring the efficacy of certain ASDs have, for example, shown a possible improved outcome with PER for PWE older than 65[10] or for PWE with brain tumor-related epilepsy[11]. Despite the fact that PWE who have had previous resection or/and VNS implantation represent a significant percentage of drug-resistant epilepsy and are often enrolled in clinical trials, outcomes in these ‘super-refractory’ cohorts are not usually analyzed separately.

Previous observational studies show significant variability in the $\geq 50\%$ responder rate to PER ranging from 12.8% to 57.5%[7-10, 12-18]. In this study, the $\geq 50\%$ responder rate to PER was significantly higher for PWE who have undergone surgical resection (52.8%) than those with VNS (16.9%). Most observational studies do not provide information for these subgroups but reduced efficacy of PER in PWE with VNS was mentioned in a study where $\geq 50\%$ responder rate was significantly lower for PWE with VNS compared to those without VNS (23.1% vs 45.2%)[9]. Investigation of a cohort that included 4 PWE with VNS highlighted that 3 showed no change in seizure frequency and one had $< 50\%$ improvement[19].

Outcomes of treatment with PER in PWE and previous resection are presented in the supplementary data of a recent study where this subgroup showed a $\geq 50\%$ responder rate of 30% and an additional 16.6% were seizure-free at 6 months[17]. Interestingly, the efficacy of PER was higher for PWE with temporal lobe epilepsy (TLE) and this was confirmed for the subgroup of PWE with resection and TLE who achieved $\geq 50\%$ responder rate of 64.3%[17]. Regression analysis did not reveal an impact of previous epilepsy surgery on clinical response[17].

These study data do not allow for a complete explanation of the difference in efficacy between PWE treated by resection and VNS. While matched for basic demographics, the cohorts are intrinsically different. Candidates for epilepsy surgery suffer mainly from intractable focal epilepsy, while those undergoing VNS implantation may have refractory generalised epilepsy, refractory focal epilepsy not suitable for surgery or other significant co-morbidities. For example, a significant number of people who proceed to VNS implantation have intellectual disability and this population is less represented in surgical case series. ~~The concurrent ASD medication does not add in the explanation since the difference in the response between the 2 groups remained within those taking EI.~~ Concurrent ASD medication does not seem to necessarily be contributory since the difference in the response between the 2 groups persisted within those taking EI

4.1. Side Effects (SEs)

Treatment-related SEs with PER were reported in 77% (severe SE in 8.9%) of the patients with focal epilepsy from a pooled analysis of 3 phase III clinical trials, but also in 66.5% of the patients receiving placebo[6]. Observational studies show a SE incidence between 41.6% and 68% [7-10, 13, 16, 18]. Only two studies show a lower percentage of SE at 32%[14] and 26%[17]. SEs, with or without lack of efficacy, are commonly the main reason for discontinuation, accounting for up to 87.1% of the people who stopped PER in one study[9]. In our cohort, the percentage of PWE who withdrew owing to SE appears slightly lower (44.8% and 41.1% for PWE with resection and VNS respectively) possibly owing to slower titration of PER in real world settings compared to clinical trials

4.2. Dose responses of PER to seizure outcome and side effects

Pooled dose-response analysis from phase III studies (304, 305) and extension 307 showed improved efficacy for PWE that increased from 8mg to 12mg during the extension study with a median percent change in seizure frequency from -32.4% at 8mg to -44.2% at 12mg, a dose effect not observed in phase III studies alone[20]. This dose-response relation appears equivocal in the observational studies[7-9]. Intriguingly, our cohort of people with ongoing seizures after surgical intervention, showed better outcomes with PER doses ≥ 8 mg. The effect was more pronounced for PWE with VNS where from 11 responders eight were taking doses > 8 mg.

SE did not appear dose-related in our groups and people taking PER at doses < 8 mg presented more likely to report SE in both groups although the difference between groups was not significant. The exact reasons for these findings are uncertain although the cohort represents some of the most refractory PWE and may, therefore, be more accepting of SEs. These individuals are also more likely to be taking polytherapy that might have affected PER levels enabling them to tolerate higher doses.

5. Limitations

The study is limited by being of retrospective design although this is somewhat mitigated by numbers included and the multi-centre approach. Nonetheless, although the overall cohort size is not insubstantial, each group (surgical resection; VNS) was very heterogeneous precluding sub-group analysis. We would, for example, have wished to examine if specific surgical pathologies or seizure locations correlated with better response to PER. Details about concomitant medication were also often missing preventing analysis of whether side effects could be related to drug combinations. Finally, it was very difficult to judge the dose at which initial improvement to PER was noted.

6. Conclusion

This study shows that adjunctive PER in two super-refractory epilepsy groups, namely people with ongoing seizures after VNS or previous epilepsy surgery, can be beneficial – perhaps particularly in people who continue to experience seizures after surgical resection. Higher doses of PER are also likely to be better tolerated in this group and the safety profile did not differ significantly from previous observational studies on PER. This may suggest that it is likely more reasonable to gradually up-titrate PER above 8mg daily in people with seizures after surgical interventions. More specifically, the majority of PWE with VNS who responded to PER, did so at higher doses and this information could inform clinical practice going forwards. Sub-group analysis of clinical trial data pertaining to people with super-refractory epilepsy is advocated, particularly for novel AEDs.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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	VNS N = 77	Post-Resective-Surgery N = 36	p-value
A: Demographics			
Male	40 (52%)	13 (36.1%)	0.16
Female	37 (48%)	23 (63.9%)	
Age (mean [years (1SD)])	42.86 (13.44)	44.64 (12.40)	0.5
Age of onset (mean [years (1SD)])	14.56 (11.03)	14.79 (10.29)	0.92
Mean Total Antiepileptic Medications at time of perampanel initiation (SD)	2.76 (1.1)	2.43 (0.51)	0.09
Mean Total Medications tried prior to perampanel (SD)	5.89 (3.3)	6.69 (4.37)	0.28
Seizure Type Prevalence* (%)			
Focal aware	58 (75.3%)	27 (75%)	0.43
Focal impaired awareness	18 (23.4%)	15 (41.7%)	
Bilateral tonic clonic	40 (52%)	18 (50%)	
Absence	4 (5.2%)	1 (2.8%)	
Myoclonic	1 (1.3%)	0 (0%)	-
Tonic	9 (11.7%)	0 (0%)	-
Astatic	11 (14.3%)	0 (0%)	-
Atonic	4 (5.2%)	0 (0%)	-
Focal (not further specified)	3 (3.9%)	0 (0%)	-
Perampanel Cessation/Withdrawal <6 Months after Initiation (%)			
Withdrawn prior to 6 months	15	6	
Perampanel Cessation/Withdrawal >6 Months after Initiation (%)			
Withdrawn	43 (55.8%) 21 (27.3%) Undocumented	16 (44.4%) 7 (19.4%) Undocumented	0.18

Reason for Perampanel Withdrawal >6 months after Initiation					
Side Effects	23 (41.1%)	13 (81.3%)	0.1		
Increase Seizure Frequency/Severity	9 (21%)	1 (6.3%)	*		
Ineffective	19 (44.2%)	7 (43.8%)	-		
Other/Unknown	3 (7%)	0 (0%)	-		
Mean time (months) prior to withdrawal (SD)	19.48 (±12.29) (N = 25)	14.55 (±7.47) (N = 11)	0.23		
Perampanel Doses (mg)					
Median Dose (SD)	6 N = 59	6 N = 33	1		
B: Effect of perampanel on seizure frequency			N _{total}		
f↔	32 (41.56%)	9 (25.00%)	41		
f↑	14 (18.18%)	5 (13.89%)	19		
f↓<50%	18 (23.38%)	3 (8.33%)	21		
f↓≥50%	13 (16.88%)	19 (52.78%)	32		
N _{total}	77	36	113		
C: Aggregated effect of PER on seizure frequency at 6 months			N _{total}		
f↓<50%	50 (79.4%)	12 (38.7%)	62		
f↓≥50%	13 (20.6%)	19 (61.3%)	32		
N _{total}	63	31	94		
D: Effect of perampanel dose on seizure outcomes					
	VNS ≤8mg	VNS ≥8mg	Post-Resective-Surgery <8mg	Post-Resective-Surgery ≥8mg	N _{total}
f↔	14 (43.75%)	11 (40.74%)	6 (40%)	3 (16.67%)	34
f↑	8 (25%)	3 (11.11%)	1 (6.67%)	4 (22.22%)	16
f↓<50%	7 (21.88%)	5 (18.52%)	2 (13.33%)	1 (5.56%)	15
f↓≥50%	3 (9.38%)	8 (29.63%)	6 (40%)	10 (55.56%)	27
N _{sum}	32	27	15	18	92
N _{total}	59		33		92
E: Effect of PER dosing and incidence of side effects					
Dose (mg)	VNS		Post-Resective-Surgery		N _{total}
<8	21		13		34

		(35.59%)	(39.39%)	
≥ 8		16 (27.12%)	9 (27.27%)	25
N _{total}		37	22	59
F: Medication-Specific Outcomes				
ASM Medication		VNS	Post-Resective-Surgery	p-value
Enzyme Inducer (EI) + PER	f_{\leftrightarrow}	16 (80%)	4 (20%)	0.14
	f_{\uparrow}	6 (66.6%)	3 (33.3%)	1
	$f_{\downarrow < 50\%}$	7 (100%)	0 (0%)	0.08
	$f_{\downarrow \geq 50\%}$	6 (37.5%)	10 (62.5%)	**
Sodium Valproate (SV) + PER	f_{\leftrightarrow}	5 (100%)	0 (0%)	-
	f_{\uparrow}	2 (66.6%)	1 (33.3%)	-
	$f_{\downarrow < 50\%}$	2 (66.6%)	1 (33.3%)	-
	$f_{\downarrow \geq 50\%}$	1 (100%)	0 (0%)	-
EI + SV + PER	f_{\leftrightarrow}	0	0	-
	f_{\uparrow}	3 (100%)	0 (0%)	-
	$f_{\downarrow < 50\%}$	2 (100%)	0 (0%)	-
	$f_{\downarrow \geq 50\%}$	0 (0%)	1 (100%)	-

Table 1: Summary characteristics across people taking perampanel after resective surgery or VNS implantation

A) Group demographics and seizure types in VNS and surgical resection groups (PRS). *For each seizure type; multiple seizure types may be present in the same patient. The focal impaired awareness seizure group was used as the expected frequency for baseline comparison in the Fisher exact test with the frequency of other seizure types compared against it. “-” denotes where the seizure type prevalence could not be compared due to insufficient data. ** = $p < 0.01$. * = $p < 0.05$. People were allowed to cite more than one reason for PER withdrawal.

B) Contingency table of patients experiencing an increase (f_{\uparrow}), decrease $< 50\%$ ($f_{\downarrow < 50\%}$), decrease $\geq 50\%$ ($f_{\downarrow \geq 50\%}$) or no change (f_{\leftrightarrow}) in seizure frequency when treated with perampanel post-resection (Surgery) or VNS insertion. The 2x4 Fisher exact statistic p-value was < 0.001 .

C) Comparison of change in seizure frequency at 6 months post-commencement of perampanel. The $f_{\downarrow < 50\%}$ group contains those who experienced either no change in seizure frequency or less than 50% reduction in seizure frequency. $f_{\downarrow \geq 50\%}$ denotes those who experienced 50% or greater reduction in seizure frequency. This table does not include those that demonstrated an increase in seizure frequency. The 2x2 Fisher exact statistic (p-value) was < 0.01 . Percent of frequency (%) denotes the row frequency percentage.

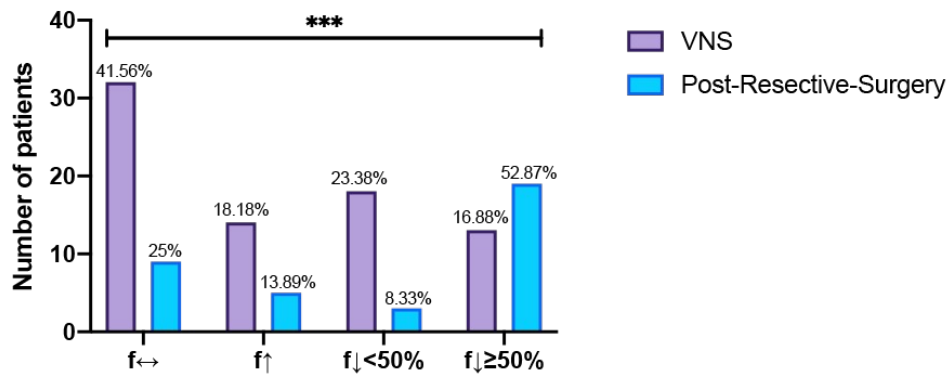
D) Dosage of perampanel in patients post-VNS/resective surgery. VNS = Vagus Nerve Stimulator Insertion cohort, Surgery = surgical resection cohort. $< 8\text{mg}$ and $\geq 8\text{mg}$ denotes the perampanel cut-off values for each group. The percent (%) signifies the percentage of the column total. In the VNS group, 18 patients were missing a dosage and from the surgical resection group 3 patients were missing a dosage. $p = 0.06$.

E) Comparison of side effect prevalence at varying doses of perampanel. Side effect information was not available for all cases. Fisher exact statistic p-value = 1.

F) Comparison of the effect of different antiseizure medications (ASM) on seizure frequency when combined with PER. “—” denotes not enough values for adequate statistic testing. EI; Enzyme Inducer, SV; Sodium Valproate.

A

Effect of Perampanel on Seizure Frequency



B

Effect of Perampanel Dose on Seizure Frequency

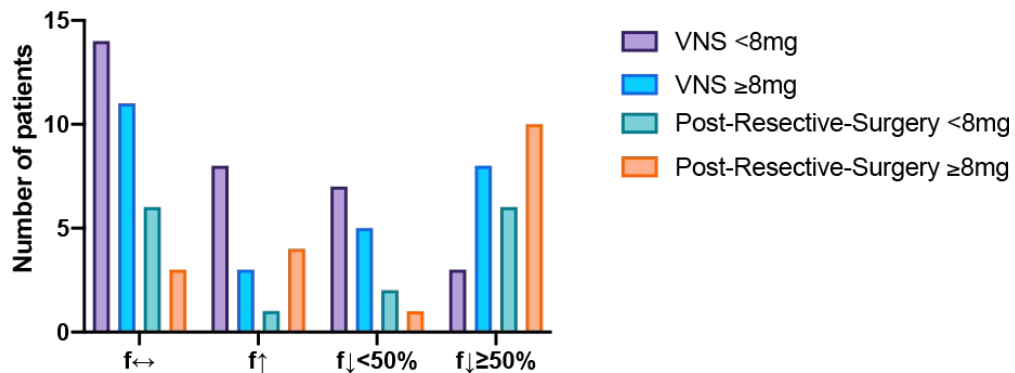


Figure 1: Efficacy of perampanel in people with ongoing seizures post surgical intervention

- A) Patients in the VNS group experienced more unchanged seizure frequency and seizure frequency increases than those in the post-resective-surgery group, who more often experienced a seizure reduction of either <50% or ≥50% with perampanel (***) (***) = Fisher exact p-value <0.001) $f_{\downarrow < 50\%}$ denotes <50% seizure frequency reduction, $f_{\downarrow \geq 50\%}$ denotes ≥ 50% seizure frequency reduction. Percentages reflect the percentage of patients within each group (VNS or post-resective surgery).
- B) Perampanel doses ≥8mg associated with higher numbers of patients experiencing a decrease in seizure frequency of ≥50% in people who had undergone surgical resection as well as those that had VNS implantation (p<0.01).