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Retention of perampanel in adults with pharmacoresistant epilepsy at a single tertiary care center

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ABSTRACT

Rationale: Observational data on antiepileptic drugs (AEDs) inform about their use in clinical practice. We describe our clinical experience with perampanel (PER) in a large UK tertiary epilepsy center.
Methods: Adults initiated on PER between October 2012 and March 2015 were followed until they discontinued PER or 10 September 2016. Data on epilepsy syndrome, duration, seizure types, concomitant and previous AED use, PER dosing, efficacy and side effects were recorded. Efficacy was categorized as temporary or ongoing (at last follow-up) seizure freedom, ≥50% seizure reduction, or other benefit (e.g. No convulsions or daytime seizures). These categories were mutually exclusive except for people with temporary seizure freedom.
Results: 391 received a PER prescription, five of whom never took it. No follow-up data were available for ten. 83% had focal epilepsy. People were prescribed PER in addition to 1–7 (Interquartile range [IQR] 2, 2, 3) AEDs and had previously used up to 18 (IQR 5, 7, 10) AEDs.
Total exposure was 639 patient/years. Retention rates were 60.4% at one year, 48.3% at two years, and 42.7% at three years. 19 (5%) people reported seizure free periods lasting at least six months. A ≥50% reduction in seizures lasting at least six months was reported by 76 people (20%), and marked improvement for ≥6 months was seen in 52 (14%). Five (1%) were taken off other AEDs and continued on PER monotherapy for 4–27 months. Seizures were aggravated in 57 (15%). Somatic side effects were reported by 197 (52%), mostly CNS. Mood changes, irritability or challenging behavior were reported by 137 (36%). PER was discontinued by 211 (56%) due to adverse effects (39%), inefficacy (26%), or both (35%). No idiosyncratic adverse events were seen.
Conclusion: PER resulted in some benefit in 40% of those exposed. Adverse effects on mental health and on balance were common and should be discussed with people before initiating PER.

1. Introduction

Perampanel (PER) is a recently introduced AED which acts as a non-competitive antagonist at AMPA receptors in the brain, sthereby reducing neuronal excitability [1]. PER was licensed as add-on treatment in focal epilepsy following results from three randomized controlled trials in people with pharmacoresistant epilepsy [2–4].

Regulatory trials establish whether an AED is effective, but do not inform about its use in the "real-life" population with epilepsy, many of whom might not meet the inclusion criteria for these trials for a number of reasons. We have evaluated the use of newly introduced AEDs over the past 20 years [5–10]. Here, we present a similar observation on the use of PER.

2. Patients and methods

Adults 17 years and older with epilepsy who received their first prescription for PER at the epilepsy specialist clinics at National Hospital for Neurology and Neurosurgery (Queen Square and Chalfont sites) between 1 October 2012 and 31 March 2015 were identified using the hospital's central pharmacy database and the departmental database. People started on PER elsewhere were excluded to avoid referral bias. Data regarding epilepsy syndrome, seizure types, age at onset of epilepsy, psychiatric comorbidity (if listed in records or inferred by use of antidepressant or antipsychotic medications), presence of learning

Abbreviations: AED, antiepileptic drug; IQR, interquartile range; PER, perampanel; SD, standard deviation; SUDEP, sudden unexplained death in epilepsy.

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disability, and use of current and previous AEDs, date of starting and stopping (where applicable) PER, maximum attained dose and maintenance dose were extracted from records. All started PER as add-on treatment. The starting dose was 2 mg per day and was typically increased every two to four weeks by 2 mg as tolerated. At our center, people with epilepsy are typically seen every six months, though they are encouraged to make phone contact in between if needed. All encounters with epilepsy care providers were analyzed to assess effect on seizure frequency and severity, adverse effects, and reasons to discontinue PER where applicable. Effect on seizures was categorized as seizure freedom for >5 times the average interval in between seizures during the previous year, a reduction in seizures by 50% or more, any other marked improvement in the assessment of either the individual or the physician, or worsening of seizures. Examples of marked improvement were cessation of convulsions, significant shortening of seizure or postictal confusion duration or reduction in seizure related falls or injuries. These categories were mutually exclusive except for periods of temporary seizure freedom (i.e. a person who reported initial seizure freedom of six months, followed by >50% reduction in seizure freedom for 12 months, appeared in both categories). We only considered beneficial effects lasting six months or longer in the analysis to avoid the regression to mean phenomenon [11]. Seizure aggravation was noted if there was a significant increase in seizure frequency or seizure related morbidity. People were followed until they discontinued PER; data were censored on 10 September 2016 for those continuing on PER. Current AED use was assessed on the day of starting PER; i.e. changes in AEDs other than PER were not captured. Three people underwent temporal lobe resections after starting PER. Improvement following surgery was not attributed to PER. This exercise was approved as an audit, and no ethics approval was necessary.

Data were collected in a Microsoft Excel Spreadsheet. Statistical analysis was performed using SPSS 16 (SPSS Inc., Chicago, IL) using descriptive statistics, Fisher's exact test, Mann–Whitney tests, Kaplan–Meier Survival analysis, and Cox regression analysis as indicated in the manuscript.

3. Results

3.1. Baseline characteristics and dosing

391 people received a prescription for PER between 22 October 2012 and 31 March 2015. For five, there was no subsequent evidence that they ever took the drug. No follow-up data were available for ten people. The analysis thus includes 376 adults who took PER for a period of 4–1389 days (censored), a total of 639 patient-years exposure. Demographic variables are given in Table 1. People were prescribed PER in addition to 1–7 (IQR 2, 2, 3) AEDs and had documented use of 1–18 (IQR 5, 7, 10) further AEDs. Table 2 lists AEDs used in addition to PER in at least 5% of people.

This is correct however I suggest that the "mg" is placed consistently within the sentence after the IQR, i. e."The maximum attained dose of PER was 2-16 (IQR 4, 8, 10) mg in all people, and 1-14 (IQR 6, 8, 10) mg in those who continued the drug at last follow up. (Table 3). Men attained a higher maximum dose than women, and people on at least one enzyme-inducing AED (carbamazepine, phenytoin, phenobarbitone, primidone, topiramate) at the time of PER initiation attained a higher maximum dose of PER compared to those on no enzyme-inducing AEDs. Those who reported side effects attained lower maximum doses than those who did not.

3.2. Benefits of perampanel

19 people (5%) reported periods of seizure freedom lasting 6 months or more. This benefit was temporary for up to 19 (median 9) months in ten, and ongoing at last follow-up for up to 38 (18) months in nine. A reduction in seizure frequency by >50% for 6 months or longer was seen in 76 (20%), temporary for up to 36 (17) months in 31 and ongoing at last follow-up for up to 42 (28) months in 45. A marked improvement for a minimum of 6 months was noted by 52 people (14%), temporary for up to 33 (12) months in 12 and ongoing at last follow-up for up to 41 (24) months in 40. 57 people (15%) reported seizure aggravation resulting in discontinuation of PER in most cases and significant reduction of the dose in the remaining. Five people discontinued other AEDs and converted to PER monotherapy. People who reported periods of seizure freedom lasting six months or more had tried fewer AEDs (mean 7.4, median 6, range 1–13) than those who did not report this benefit (mean 10.1, median 10, range 2–21, $p = 0.003$). There were no differences in the number of previously failed AEDs for the subgroups who reported seizure reduction by 50% or more for six months or longer, or those who reported "marked improvement" for six months or longer, versus those who did not.

Table 1
Demographic characteristics of people in the cohort.

Gender (female)	219	58%
Age when starting PER (years)	32, 42, 50 (IQR)	17–82 (range)
Age at epilepsy onset (years)	5, 12, 19 (IQR)	First year of life–79
Psychiatric history	101	27%
Learning disability	68	18%
Focal epilepsy	314	83%
Symptomatic	193	51%
Cryptogenic	121	32%
Generalized epilepsy	58	16%
Symptomatic	26	7%
Cryptogenic	25	7%
Idiopathic	7	2%
Unclassified	4	1%
Number of AEDs previously tried (excluding current AEDs) with evidence in electronic medical records	7 (median)	0–18 (range)
Number of AEDs previously tried (including current AEDs)	10 (median)	1–21 (range)
Number of concomitant AEDs		
One	52	14%
Two	137	36%
Three	121	32%
Four or more	66	18%

3.3. Adverse events on perampanel

197 people (52%) reported side effects, largely drowsiness, dizziness, and unsteadiness. A negative effect on mental health (worsening of mood, increased irritability, or challenging behavior) was observed in 137 (36%). One man required hospitalization for a psychotic episode shortly after starting PER. One man got arrested and another one cautioned for aggressive behavior. No idiosyncratic side effect was seen. There were two deaths in the cohort, one from myocardial infarction, the other from complications of longstanding pulmonary hypertension.

Table 2
Antiepileptic drugs used at time of initiating perampanel in at least 5% of the cohort.

Antiepileptic drug	N	%
Carbamazepine	143	38
Levetiracetam	133	35
Clobazam	117	31
Lamotrigine	85	23
Lacosamide	75	20
Zonisamide	65	17
Sodium valproate	64	17
Oxcarbazepine	62	17
Phenytoin	42	11
Topiramate	41	11
Pregabalin	32	9
Clonazepam	22	6
Phenobarbitone	19	5