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Research Paper

Effectiveness and safety of perampanel by concomitant antiseizure medications: Insights from the real-world PERMIT Extension study

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ABSTRACT

The PERMIT Extension study is the largest pooled analysis of perampanel (PER) clinical practice data to date. A *post-hoc* analysis of PERMIT Extension assessed the effectiveness and tolerability of PER with different concomitant antiseizure medication (ASM) regimens. Effectiveness was assessed by evaluating responder and seizure freedom rates at the last observation for each participant ('last visit'), and tolerability was assessed by evaluating adverse events. The analysis included 5144 people with epilepsy who had only focal (n = 4347) or only generalised (n = 797) seizures when PER was initiated, and whose type of concomitant ASM regimen at that time was known. Effectiveness and tolerability varied considerably depending on the pharmacology and mechanism of action (MoA) of concomitant ASM regimens. For example, in individuals with focal seizures receiving only one concomitant ASM at baseline, seizure freedom rates were significantly higher if the concomitant ASM was one that binds to synaptic vesicle glycoprotein 2A (SV2A) versus one that does not bind to SV2A (41.7 % vs. 24.8 %; $p < 0.001$), and significantly lower if the concomitant ASM was a sodium channel blocker versus a non-sodium channel blocker (23.2 % vs. 35.6 %; $p < 0.001$); whereas, in those with generalised seizures receiving one concomitant ASM at baseline, there were no significant differences in seizure freedom rates according to the concomitant ASM's MoA. In individuals with focal and generalised seizures, tolerability appeared to be less affected by the pharmacology and MoA of concomitant ASM regimens. The findings from this study may help inform the use of rational polytherapy in clinical practice.

Abbreviations: AE, adverse events; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; ASM, antiseizure medication; CI, confidence interval; EIASM, enzyme-inducing concomitant ASM; FAS, Full Analysis Set; non-EIASM, non-enzyme-inducing concomitant ASM; IQR, interquartile range; MoA, mechanism of action; PER, perampanel; SD, standard deviation; SV2A, synaptic vesicle glycoprotein 2A.

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1. Introduction

With the current availability of approximately 30 antiseizure medications (ASMs) with a variety of mechanisms of actions (MoAs) [1,2], there has been an increased focus on the concept of 'rational polytherapy' as a means of ensuring that individuals with epilepsy receive the most appropriate and effective treatment, while minimising the drug burden and associated risk of tolerability problems, thereby increasing the likelihood of long-term retention and treatment success [3–7]. Rational polytherapy consists of combining ASMs that not only have pharmacological profiles with minimal potential for drug–drug interactions but also different MoAs with potentially synergistic effects [3–7]. Information is therefore required concerning the effectiveness and tolerability of different ASM combinations in order to inform treatment decisions in clinical practice.

Perampanel (PER) is an ASM with a novel MoA, acting as a highly selective, noncompetitive α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor antagonist, with broad-spectrum potential for treating a variety of seizure types [8–10]. PER is approved for the treatment of focal seizures and generalised tonic-clonic seizures in people with idiopathic generalised epilepsy [11,12], and both clinical trials and clinical practice studies have demonstrated its efficacy and generally good tolerability [13–18]. The PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) Extension study is the largest pooled analysis of PER clinical practice data conducted to date, having included over 6800 individuals treated with PER [19]. PERMIT Extension participants were treated with PER in combination with a wide range of concomitant ASMs [19]. The current study was a *post-hoc* analysis of PERMIT Extension undertaken to assess the effectiveness and tolerability of PER according to different concomitant ASM regimens.

2. Methods

2.1. Study design

PERMIT Extension was a pooled analysis of PER clinical practice studies, and it assessed retention on PER treatment and its effectiveness, safety, and tolerability over a follow-up duration of at least 12 months [19]. Full details of its design and inclusion/exclusion criteria have been published previously [19]. This *post-hoc* analysis included PERMIT Extension participants for whom the type(s) of baseline concomitant ASMs was known. The analysis was restricted to participants with only focal seizures or only generalised seizures at baseline; those with both seizure types or status epilepticus were excluded. All studies included in PERMIT Extension were approved by appropriate ethics committees and performed in accordance with the 1964 Declaration of Helsinki and later amendments [20].

2.2. Study assessments

Effectiveness was assessed by evaluating the responder rate and seizure freedom rate at the last observation for each participant (*i.e.*, last observation carried forward; hereon referred to as the 'last visit'). Responder and seizure freedom rates were assessed for the subgroups with only focal and only generalised seizures at baseline in the following ways: (1) for the top five most commonly used ASM regimens at baseline; (2) according to the type of individual concomitant ASMs used by $\geq$ 1 % of the subgroups at baseline; (3) according to the MoA of the concomitant ASM in individuals treated with only one concomitant ASM at baseline (Table 1 [21]); and (4) in the subgroups treated with enzyme-inducing concomitant ASMs (EIASMs) versus non-enzyme-inducing concomitant ASMs (non-EIASMs).

Tolerability was assessed by evaluating the incidence of adverse events (AEs), AEs leading to discontinuation over 12 months, and psychiatric AEs. For the subgroups with only focal and only generalised seizures at baseline, these tolerability outcomes were assessed in the following ways: (1) incidence of AEs, AEs leading to discontinuation, and psychiatric AEs in the overall subgroups (focal, generalised); (2) incidence of AEs and AEs leading to discontinuation over 12 months for the top five most commonly used ASM regimens at baseline; (3) incidence of AEs according to the type of individual ASMs used by $\geq$ 1 % of the subgroups at baseline; (4) incidence of AEs according to the MoA of the concomitant ASM in individuals treated with only one concomitant ASM at baseline (Table 1 [21]); (5) incidence of AEs in the subgroups treated with EIASMs versus non-EIASMs; (6) incidence of psychiatric AEs in the subgroups with versus without psychiatric comorbidity at baseline; and (7) incidence of psychiatric AEs in the subgroups treated with versus not treated with concomitant levetiracetam.

In addition, PER dosing was assessed in the total population and subgroups with only focal and only generalised seizures at baseline, as well as in the subgroups treated with EIASMs versus non-EIASMs.

Table 1
Categorisation of ASMs by MoA [21].

MoA	ASMs
Sodium channel blocker	Carbamazepine; eslicarbazepine acetate; lacosamide; lamotrigine; oxcarbazepine; phenytoin; rufinamide
GABAergic	Clobazam; clonazepam; diazepam; phenobarbital; primidone; tiagabine; vigabatrin
Calcium channel modulator	Ethosuximide; gabapentin; pregabalin
Potassium-enhancing drug	Retigabine
SV2A	Brivaracetam; levetiracetam
Mixed MoA	Felbamate; stiripentol; topiramate; valproate; zonisamide

ASM, antiseizure medication; GABA, gamma-aminobutyric acid; MoA, mechanism of action; SV2A, synaptic vesicle glycoprotein 2A.

2.3. Statistical methodology

The Full Analysis Set (FAS) included all people with epilepsy treated with PER. The Effectiveness and Tolerability populations were defined as previously reported in the PERMIT Extension primary publication [19]. A descriptive analysis of qualitative and quantitative variables was performed. Qualitative variables were assessed as absolute frequencies and percentages, and quantitative variables were summarised as the mean, standard deviation (SD), median, minimum and maximum values, 95 % confidence interval (CIs) or interquartile range (IQR), and number of valid cases. PER dosing at initiation and the last visit were compared for the subgroups being treated at baseline with EIASMs versus non-EIASMs using the Mann-Whitney test. Effectiveness (responder rate and seizure freedom rate) and the incidence of AEs were compared between the subgroups of participants treated with versus without individual types of concomitant ASMs, and with versus without concomitant ASMs with particular MoAs, using the Chi-square test or Fisher's exact test, as appropriate. Effectiveness and the incidence of AEs were compared between the subgroups of participants treated with EIASMs versus non-EIASMs using the Chi-square test. The incidence of psychiatric AEs was compared between the subgroups of participants with versus without psychiatric comorbidity at baseline, and the subgroups treated with versus without concomitant levetiracetam, using the Chi-square test. For all assessments, separate analyses were performed for the participants with only focal and only generalised seizures at baseline.

3. Results

3.1. Study population

The FAS included 5144 people with epilepsy from PERMIT Extension who had only focal or only generalised seizures when PER was initiated, and whose type of concomitant ASM regimen at the time of PER

initiation was known. Of these, 4347 (84.5 %) had only focal seizures and 797 (15.5 %) had only generalised seizures. The Effectiveness Population included 3708 individuals (focal, n = 3230; generalised, n = 478) and the Tolerability Population included 4754 individuals (focal, n = 3980; generalised, n = 774).

In the overall study population, the mean (SD) age was 37.8 (16.2) years, 50.7 % were female, and 24.8 % had psychiatric comorbidity at baseline (Table 2). The focal seizures subgroup was older (mean [SD] age, 39.1 [15.9] vs. 30.3 [15.5] years), had a longer duration of epilepsy (mean [SD], 23.2 [16.1] vs. 17.6 [13.5] years), and had been treated with more previous ASMs (mean [SD], 5.1 [3.7] vs. 3.5 [3.2]), in comparison with the generalised seizures subgroup.

3.2. ASM treatment

In the overall study population, the mean (SD) PER dose was 2.6 (1.5) mg/day at initiation and 6.2 (2.9) mg/day at the last visit. At the time of initiation, the mean (SD) PER dose was statistically significantly higher in the non-EIASM versus EIASM subgroup (2.7 [1.6] vs. 2.4 [1.3] mg/day; $p < 0.001$), but at the last visit the mean (SD) PER dose was statistically significantly lower in the non-EIASM versus EIASM subgroup (5.9 [2.8] vs. 6.6 [2.9] mg/day; $p < 0.001$). In the focal seizures subgroup, the mean (SD) PER dose was 2.5 (1.5) mg/day at initiation and 6.3 (2.9) mg/day at the last visit. As in the overall population, the mean (SD) PER dose was statistically significantly higher in the non-EIASM versus EIASM subgroup at initiation (2.7 [1.7] vs. 2.3 [1.3] mg/day; $p < 0.001$), but statistically significantly lower in the non-EIASM versus EIASM subgroup at the last visit (6.0 [2.8] vs. 6.7 [2.9] mg/day; $p < 0.001$). In the generalised seizures subgroup, the mean (SD) PER dose was 2.7 (1.6) mg/day at initiation and 5.7 (2.8) mg/day at the last visit. The mean (SD) PER dose was not statistically significantly different between the non-EIASM and EIASM subgroups at either initiation (2.6 [1.4] vs. 2.9 [2.2] mg/day) or the last visit (5.7 [2.8] vs. 6.0 [3.1] mg/day).

In the overall study population, the mean (SD) number of concomitant ASMs was 2.3 (1.0), and the most commonly used concomitant ASMs (≥ 20 % of population) at baseline were levetiracetam (39.9 %), lamotrigine (25.6 %), valproate (23.3 %) and lacosamide (22.5 %) (Table 2). The mean (SD) number of concomitant ASMs was higher in the focal versus generalised seizures subgroup (mean [SD], 2.3 [1.0] vs. 2.0 [1.0]). There were also differences between the subgroups in the types of concomitant ASMs being used (see Table 2), and a greater proportion of those with focal versus generalised seizures were being treated with EIASMs at baseline (51.7 % vs. 17.8 %).

3.3. Effectiveness

3.3.1. Effectiveness according to top five most commonly used ASM regimens at baseline

In individuals with focal seizures, the five most commonly used concomitant ASM regimens at baseline were levetiracetam alone (n = 248), lamotrigine alone (n = 142), lacosamide + levetiracetam (n = 131), valproate alone (n = 113), and carbamazepine alone (n = 109). At the last visit, responder rates ranged from 42.0 % for individuals being treated with concomitant lacosamide + levetiracetam to 74.1 % for those receiving concomitant valproate alone, and seizure freedom rates ranged from 12.6 % for individuals being treated with concomitant carbamazepine alone to 41.9 % for those receiving concomitant levetiracetam alone (Fig. 1).

In individuals with generalised seizures, the five most commonly used concomitant ASM regimens at baseline were levetiracetam alone (n = 112), valproate alone (n = 57), levetiracetam + valproate (n = 43), lamotrigine alone (n = 40), and topiramate alone (n = 22). At the last visit, responder rates ranged from 71.4 % for individuals being treated with concomitant topiramate alone to 88.0 % for those receiving concomitant lamotrigine alone, and seizure freedom rates ranged from

Table 2
Demographic and baseline characteristics for the total population and the subgroups of individuals with only focal or generalised seizures at baseline (Full Analysis Set).

Characteristic	Total population	Focal seizures only	Generalised seizures only
Number of people	**N = 5144**	**N = 4347**	**N = 797**
Sex			
N[a]	5134	4338	796
Female, n (%)	2603 (50.7)	2175 (50.1)	428 (53.8)
Male, n (%)	2531 (49.3)	2163 (49.9)	368 (46.2)
Age, years			
N[a]	5090	4307	783
Mean (SD)	37.8 (16.2)	39.1 (15.9)	30.3 (15.5)
Median (range)	37.0 (0.3–97.0)	38.0 (1.2–97.0)	28.0 (0.3–85.0)
Duration of epilepsy, years			
N[a]	4557	3797	760
Mean (SD)	22.3 (18.8)	23.2 (16.1)	17.6 (13.5)
Median (range)	19.0 (0.0–82.0)	21.0 (0.0–82.0)	14.0 (0.0–77.0)
Aetiology			
N[a]	4262	3545	717
Structural, n (%)	1644 (38.6)	1594 (45.0)	50 (7.0)
Genetic, n (%)	641 (15.0)	69 (1.9)	572 (79.8)
Infectious, n (%)	88 (2.1)	80 (2.3)	8 (1.1)
Unknown, n (%)	1865 (43.8)	1778 (50.2)	87 (12.1)
Other, n (%)	24 (0.6)	24 (0.7)	0
Seizure frequency/month			
N[a]	1591	1185	295
Mean (SD)	21.4 (85.0)	17.6 (79.7)	28.7 (91.4)
Median (range)	3.3 (0.1–2370.0)	4.0 (0.1–2370.0)	1.3 (0.1–800.0)
Psychiatric comorbidity			
N[a]	3208	2489	719
Yes, n (%)	795 (24.8)	633 (25.4)	162 (22.5)
No, n (%)	2413 (75.2)	1856 (74.6)	557 (77.5)
Number of previous ASMs[b]			
N[a]	4438	3749	689
Mean (SD)	4.8 (3.7)	5.1 (3.7)	3.5 (3.2)
Median (range)	4.0 (0.0–22.0)	5.0 (0.0–22.0)	3.0 (0.0–18.0)
0 ASMs, n (%)	469 (10.6)	364 (9.7)	105 (15.2)
1 ASM, n (%)	475 (10.7)	348 (9.3)	127 (18.4)
2 ASMs, n (%)	475 (10.7)	381 (10.2)	94 (13.6)
3 ASMs, n (%)	465 (10.5)	387 (10.3)	78 (11.3)
4 ASMs, n (%)	469 (10.6)	394 (10.5)	75 (10.9)
5 ASMs, n (%)	413 (9.3)	357 (9.5)	56 (8.1)
6 ASMs, n (%)	409 (9.2)	360 (9.6)	49 (7.1)
7 ASMs, n (%)	286 (6.4)	254 (6.8)	32 (4.6)
8 ASMs, n (%)	251 (5.7)	234 (6.2)	17 (2.5)
9 ASMs, n (%)	207 (4.7)	190 (5.1)	17 (2.5)
≥10 ASMs, n (%)	519 (11.7)	480 (12.8)	39 (5.7)
Number of concomitant ASMs at baseline			
N[a]	5144	4347	797
Mean (SD)	2.3 (1.0)	2.3 (1.0)	2.0 (1.0)
Median (range)	2.0 (1–8)	2.0 (1–8)	2.0 (1–6)
1 ASM, n (%)	1285 (25.0)	990 (22.8)	295 (37.0)
2 ASMs, n (%)	1941 (37.7)	1658 (38.1)	283 (35.5)
3 ASMs, n (%)	1350 (26.2)	1205 (27.7)	145 (18.2)
>3 ASMs, (n%)	568 (11.0)	494 (11.4)	74 (9.3)
Most common[c] ASMs at baseline[d]			
N[a]	5144	4347	797
Levetiracetam, n (%)	2054 (39.9)	1682 (38.7)	372 (46.7)
Lamotrigine, n (%)	1317 (25.6)	1127 (25.9)	190 (23.8)
Valproate, n (%)	1197 (23.3)	916 (21.1)	281 (35.3)
Lacosamide, n (%)	1159 (22.5)	1052 (24.2)	107 (13.4)
Carbamazepine, n (%)	961 (18.7)	911 (21.0)	50 (6.3)
Zonisamide, n (%)	728 (14.2)	602 (13.8)	126 (15.8)
Clobazam, n (%)	694 (13.5)	627 (14.4)	67 (8.4)
Topiramate, (n%)	606 (11.8)	503 (11.6)	103 (12.9)
Oxcarbazepine, n (%)	566 (11.0)	544 (12.5)	22 (2.8)
Use of enzyme-inducing concomitant ASMs[e]			

(continued on next page)

Table 2 (*continued*)

Characteristic	Total population	Focal seizures only	Generalised seizures only
N[a]	5144	4347	797
Yes, n (%)	2390 (45.5)	2248 (51.7)	142 (17.8)
No, n (%)	2754 (53.5)	2099 (48.3)	655 (82.2)
MoA of concomitant ASMs[f]			
N[a]	5144	4347	797
Sodium channel blocker, n (%)	3785 (73.6)	3412 (78.5)	373 (46.8)
GABAergic, n (%)	1464 (28.5)	1291 (29.7)	173 (21.7)
Calcium channel modulator, n (%)	288 (5.6)	254 (5.8)	34 (4.3)
Potassium-enhancing drug, n (%)	97 (1.9)	96 (2.2)	1 (0.1)
SV2A, n (%)	2092 (40.7)	1718 (39.5)	374 (46.9)
Mixed MoA, n (%)	2293 (44.6)	1838 (42.3)	455 (57.1)

[a] Number of PWE for whom data in question were available.
[b] Including concomitant ASMs.
[c] n ≥ 10 % at least in one of the groups.
[d] Patients could receive more than one ASM.
[e] Defined as carbamazepine, eslicarbazepine acetate, oxcarbazepine, phenobarbital, phenytoin, and primidone.
[f] See Table 1 [21]. ASM, antiseizure medication; GABA, gamma-aminobutyric acid; MoA, mechanism of action; SD, standard deviation; SV2A, synaptic vesicle glycoprotein 2A.

42.9 % for individuals being treated with concomitant topiramate alone to 72.6 % for those receiving concomitant levetiracetam alone (Fig. 1).

3.3.2. *Effectiveness according to the type of individual concomitant ASMs used by ≥ 1 % of individuals at baseline*

Responder and seizures freedom rates for concomitant ASMs used at baseline by ≥ 1 % of individuals with focal seizures are shown in Fig. 2. Responder rates were significantly lower in individuals treated with versus without carbamazepine (40.3 % vs. 47.0 %; p = 0.002), clobazam (35.1 % vs. 47.4 %; p < 0.001), clonazepam (33.9 % vs. 46.2 %; p = 0.001), eslicarbazepine acetate (38.6 % vs. 46.3 %; p = 0.006), lacosamide (37.7 % vs. 47.7 %; p < 0.001), lamotrigine (39.9 % vs. 47.2 %; p = 0.001), phenobarbital (34.5 % vs. 46.6 %; p < 0.001), and retigabine (19.7 % vs. 46.0 %; p < 0.001), and significantly higher in those treated with versus without daily diazepam (64.7 % vs. 45.2 %; p = 0.023) and valproate (50.1 % vs. 44.1 %; p = 0.008) (Fig. 2**A**). Seizure freedom rates were significantly lower in individuals treated with versus without carbamazepine (9.7 % vs. 16.8 %; p < 0.001), clobazam (6.7 % vs. 16.7 %; p < 0.001), clonazepam (9.7 % vs. 15.3 %; p = 0.032), lacosamide (11.3 % vs. 16.1 %; p = 0.001), lamotrigine (11.7 % vs. 16.1 %; p = 0.002), phenobarbital (7.8 % vs. 15.7 %; p < 0.001), retigabine (1.2 % vs. 15.4 %; p < 0.001) and zonisamide (10.7 % vs. 15.6 %; p = 0.009), and significantly higher in those treated with versus without levetiracetam (17.2 % vs. 13.7 %; p = 0.007) (Fig. 2**B**).

Responder and seizures freedom rates for concomitant ASMs used at baseline by ≥ 1 % of individuals with generalised seizures are shown in Fig. 3. Responder rates were significantly lower in individuals treated with versus without carbamazepine (50.0 % vs. 74.9 %; p = 0.001), clobazam (50.0 % vs. 75.1 %; p = 0.001), lamotrigine (62.5 % vs. 75.5 %; p = 0.011) and phenobarbital (40.9 % vs. 74.4 %; p = 0.001) (Fig. 3**A**). Seizure freedom rates were significantly lower in those treated with versus without carbamazepine (35.0 % vs. 53.2 %; p = 0.027), clobazam (28.3 % vs. 54.2 %; p = 0.001), clonazepam (34.1 % vs. 53.5 %; p = 0.014), ethosuximide (21.4 % vs. 52.6 %; p = 0.028), lacosamide (34.2 % vs. 53.2 %; p = 0.025), phenobarbital (22.7 % vs. 53.1 %; p = 0.005), rufinamide (18.8 % vs. 52.8 %; p = 0.009) and topiramate (31.5 % vs. 54.2 %; p = 0.002) (Fig. 3**B**).

3.3.3. *Effectiveness according to the MoA of the concomitant ASM in individuals treated with only one concomitant ASM at baseline*

In individuals with focal seizures receiving only one concomitant ASM at baseline, responder rates were significantly higher if the concomitant ASM was one that binds to synaptic vesicle glycoprotein 2A

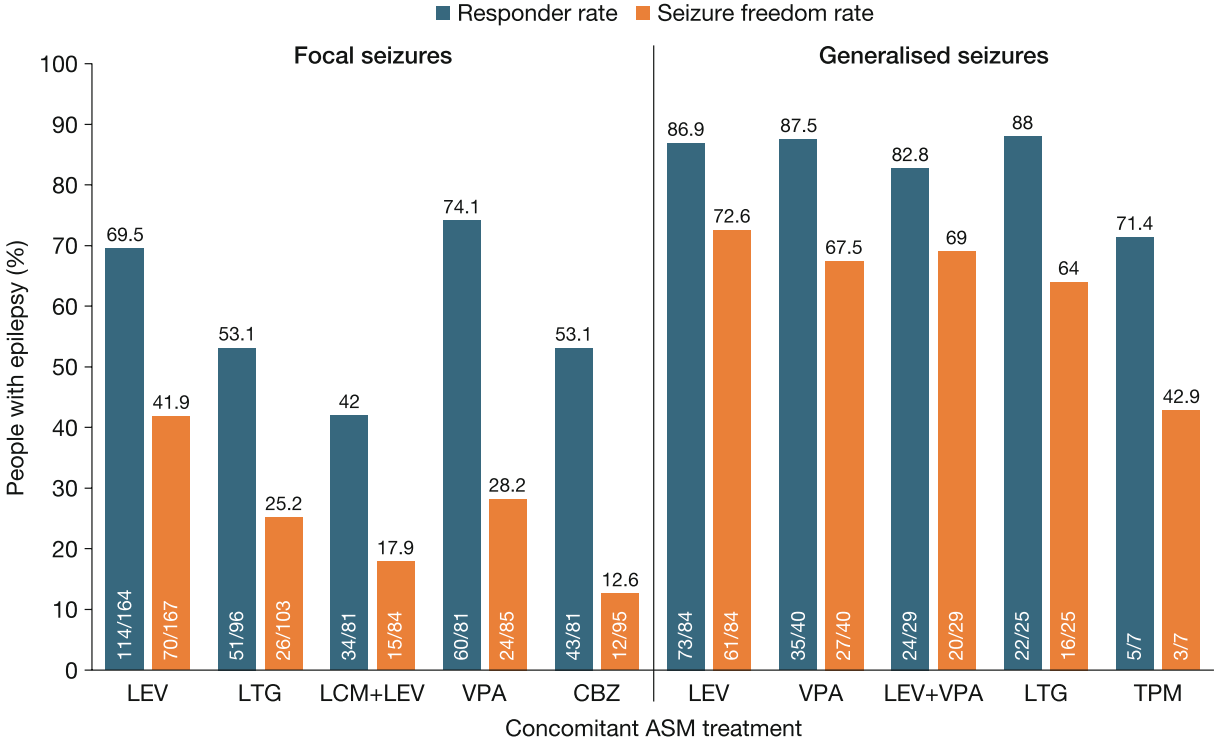

Fig. 1. Responder rate and seizure freedom rate at the last visit according to the top five most frequently used concomitant ASM treatments in subgroups with only focal or only generalised seizures (Effectiveness Population). ASM, antiseizure medication; CBZ, carbamazepine; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PER, perampanel; TPM; topiramate; VPA, valproate.

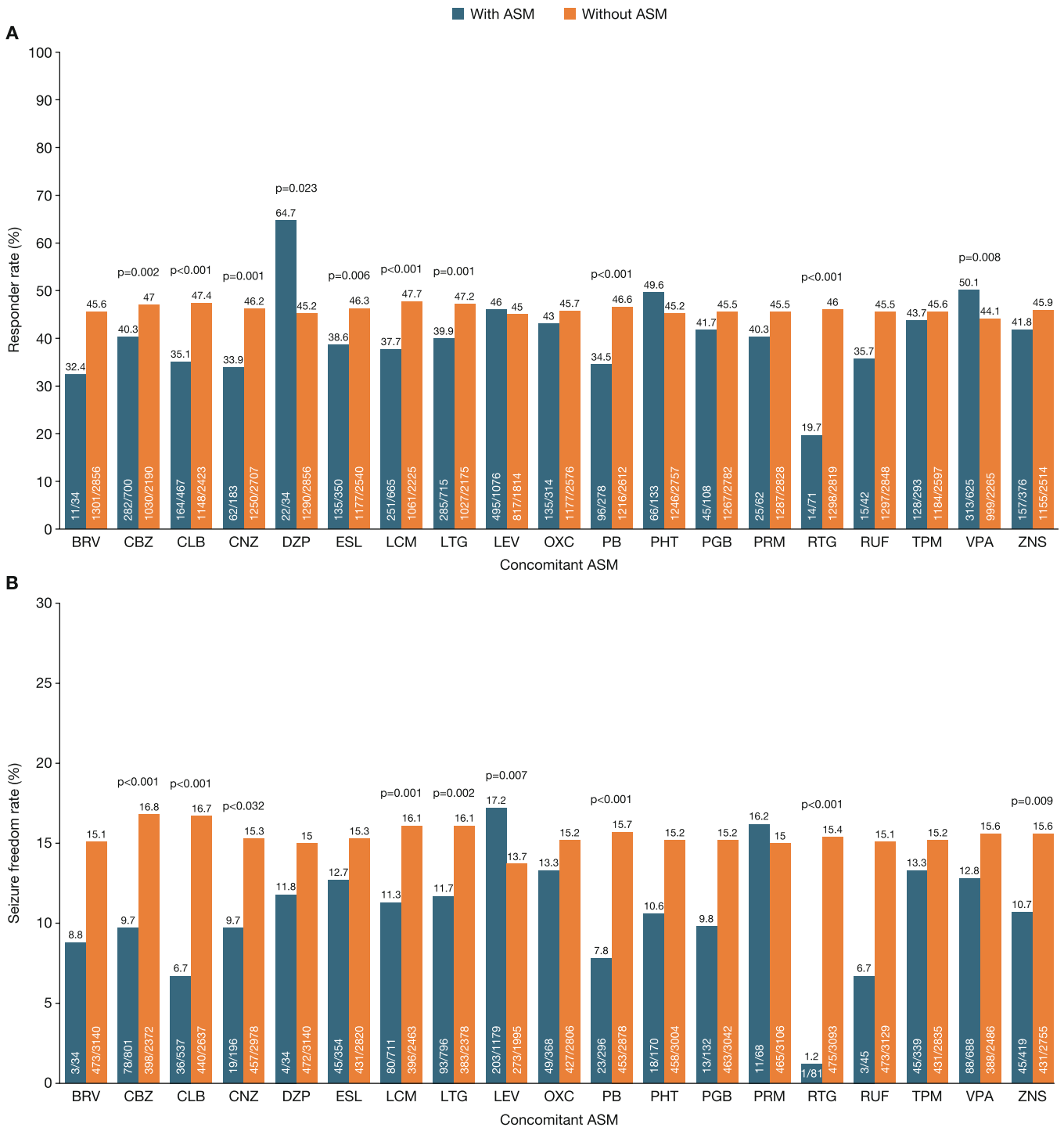

Fig. 2. Seizure frequency outcomes at the last visit in the subgroup with only focal seizures, according to the individual type of concomitant ASM: (A) Responder rate and (B) Seizure freedom rate (Effectiveness Population). Data are presented in the subgroups of people receiving PER with or without a specific ASM. Data are shown for concomitant ASMs used by ≥ 1 % of people with only focal seizures at baseline (N = 3230). ASM, antiseizure medication; BRV, brivaracetam; CBZ, carbamazepine; CLB, clobazam; CNZ, clonazepam; DZP, diazepam; ESL, eslicarbazepine acetate; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; PRM, primidone; RTG, retigabine; RUF, rufinamide; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

(SV2A) versus one that does not bind to SV2A (69.7 % vs. 59.9 %; p = 0.025), significantly higher if the concomitant ASM had a mixed MoA versus one that did not have a mixed MoA (73.3 % vs. 60.0 %; p = 0.008), and significantly lower if the concomitant ASM was a sodium channel blocker (SCB) versus one that was not an SCB (54.6 % vs. 71.2 %; p < 0.001) (Fig. 4**A**); and seizure freedom rates were significantly higher if the concomitant ASM was one that binds to SV2A versus one that does not bind to SV2A (41.7 % vs. 24.8 %; p < 0.001), and significantly lower if the concomitant ASM was an SCB versus one that was not an SCB (23.2 % vs. 35.6 %; p < 0.001) (Fig. 4**B**).

In participants with generalised seizures receiving one concomitant ASM at baseline, there were no significant differences in responder and seizure freedom rates according to the MoA of the concomitant ASM (Fig. 5).

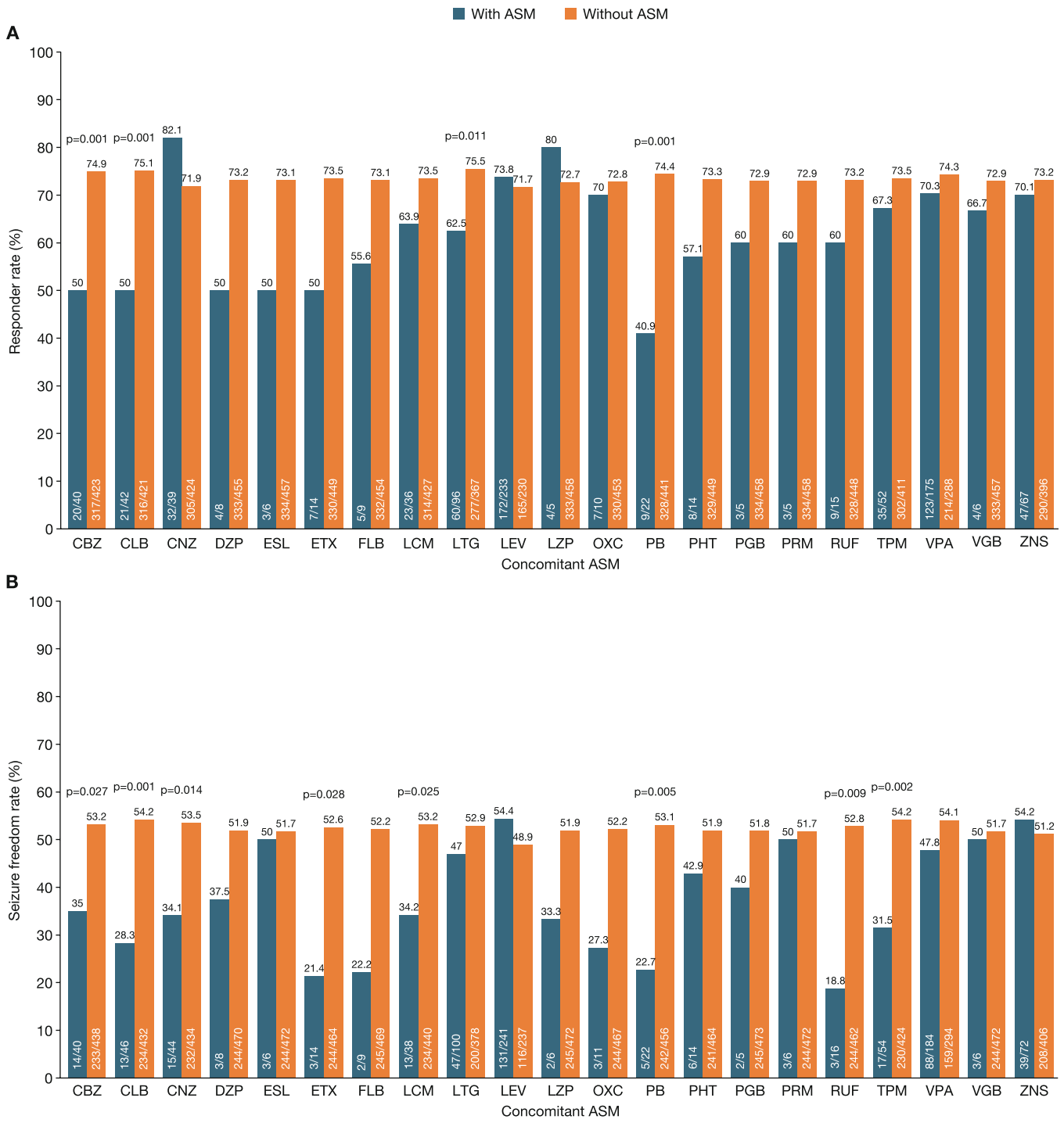

Fig. 3. Seizure frequency outcomes at the last visit in the subgroup with only generalised seizures, according to the individual type of concomitant ASM: (A) Responder rate and (B) Seizure freedom rate (Effectiveness Population). Data are presented in the subgroups of people receiving PER with or without a specific ASM. Data are shown for concomitant ASMs used by ≥ 1 % of people with only generalised seizures at baseline (N = 478). ASM, antiseizure medication; CBZ, carbamazepine; CLB, clobazam; CNZ, clonazepam; DZP, diazepam; ESL, eslicarbazepine acetate; ETX, ethosuximide; FLB, felbamate; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; LZP, lorazepam; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; PRM, primidone; RUF, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide.

3.3.4. Effectiveness in individuals treated with concomitant EIASMs versus non-EIASMs

In individuals with focal seizures, the responder rate at the last visit was significantly lower in those treated with concomitant EIASMs versus non-EIASMs (40.8 % vs. 51.3 %; $p < 0.001$), as was the seizure freedom rate (11.4 % vs. 19.7 %; $p < 0.001$) (Fig. 6). Similarly, in participants with generalised seizures, the responder rate at the last visit was significantly lower in those treated with concomitant EIASMs versus non-EIASMs (51.2 % vs. 77.6 %; $p < 0.001$), and so was the seizure freedom rate (33.7 % vs. 55.6 %; $p < 0.001$) (Fig. 6).

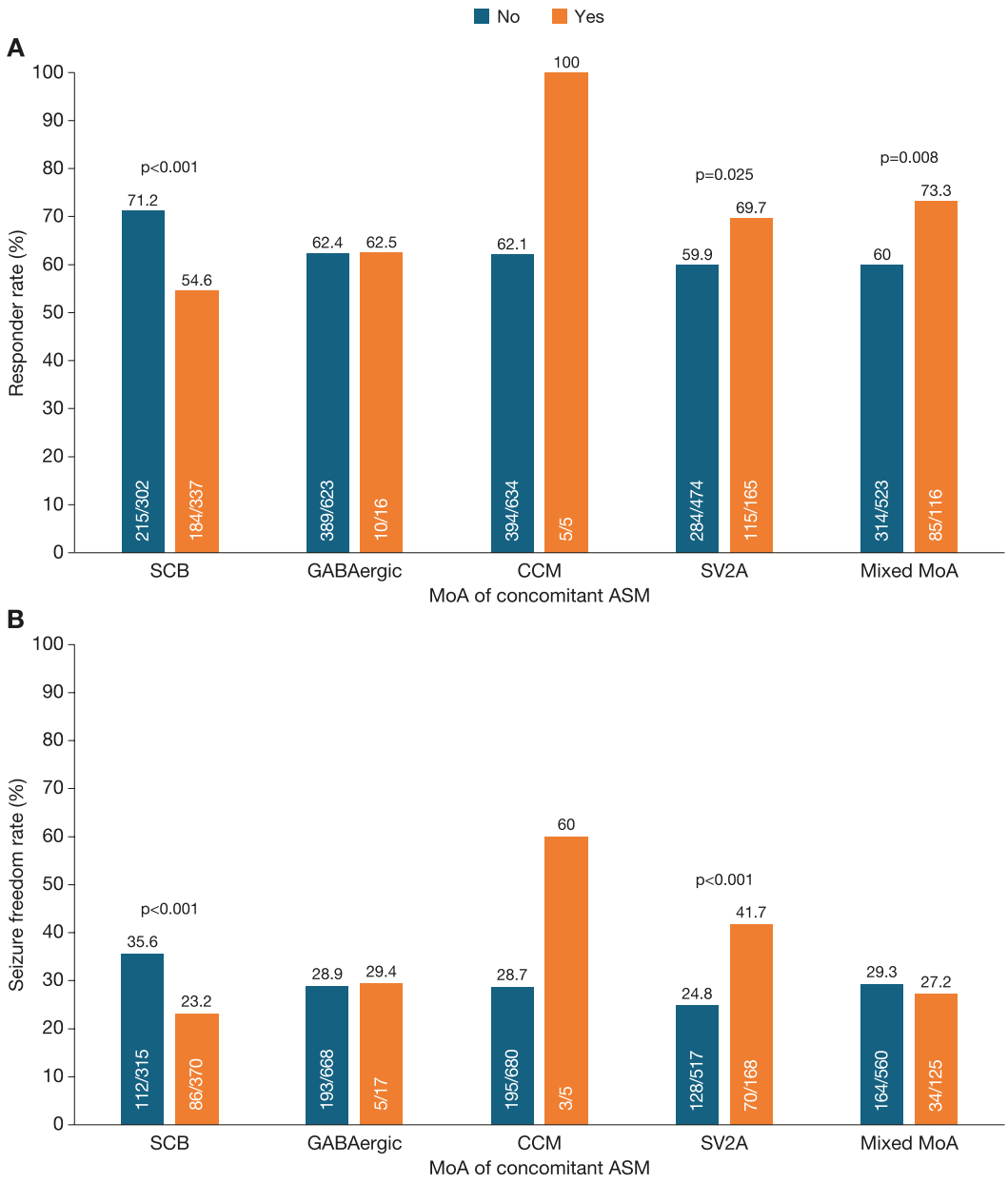

Fig. 4. Seizure frequency outcomes at the last visit in the subgroup with only focal seizures and receiving only one concomitant ASM at baseline, according to the MoA of the concomitant ASM: (A) Responder rate and (B) Seizure freedom rate (Effectiveness Population). 'No' indicates 'not treated with concomitant ASM with specified MoA'. 'Yes' indicates 'treated with concomitant ASM with specified MoA'. ASM, antiseizure medication; CCM, calcium channel modulator; GABA, gamma-aminobutyric acid; MoA, mechanism of action; PER, perampanel; SCB, sodium channel blocker; SV2A, synaptic vesicle glycoprotein 2A.

3.4. Tolerability

3.4.1. Incidence of AEs, AEs leading to discontinuation, and psychiatric AEs in the overall subgroups (focal seizures, generalised seizures)

In individuals with focal seizures, the incidence of AEs was 51.5 % (2048/3980), the incidence of AEs leading to discontinuation over 12 months was 19.4 % (610/3147), and the incidence of psychiatric AEs was 21.1 % (834/3959). In those with generalised seizures, the corresponding incidence rates were 49.1 % (380/774), 16.0 % (71/444) and 24.9 % (192/771), respectively.

3.4.2. Incidence of AEs and AEs leading to discontinuation for top five most commonly used ASM regimens at baseline

In individuals with focal seizures, the incidence of AEs ranged from 12.6 % in those treated with concomitant carbamazepine alone to 41.9 % in those receiving concomitant levetiracetam alone, and the incidence of AEs leading to discontinuation over 12 months ranged from 16.9 % for those being treated with concomitant lamotrigine alone to 20.8 % in those receiving concomitant lacosamide + levetiracetam (Fig. 7).

In participants with generalised seizures, the incidence of AEs ranged from 43.4 % in those being treated with concomitant levetiracetam alone to 53.7 % in those receiving concomitant levetiracetam + valproate, and the incidence of AEs leading to discontinuation over 12 months ranged from 3.2 % in those being treated with concomitant valproate alone to 57.1 % in those receiving concomitant topiramate alone (Fig. 7).

3.4.3. Incidence of AEs according to the type of individual concomitant ASMs used by ≥ 1 % of individuals at baseline

In individuals with focal seizures, the incidence of AEs was

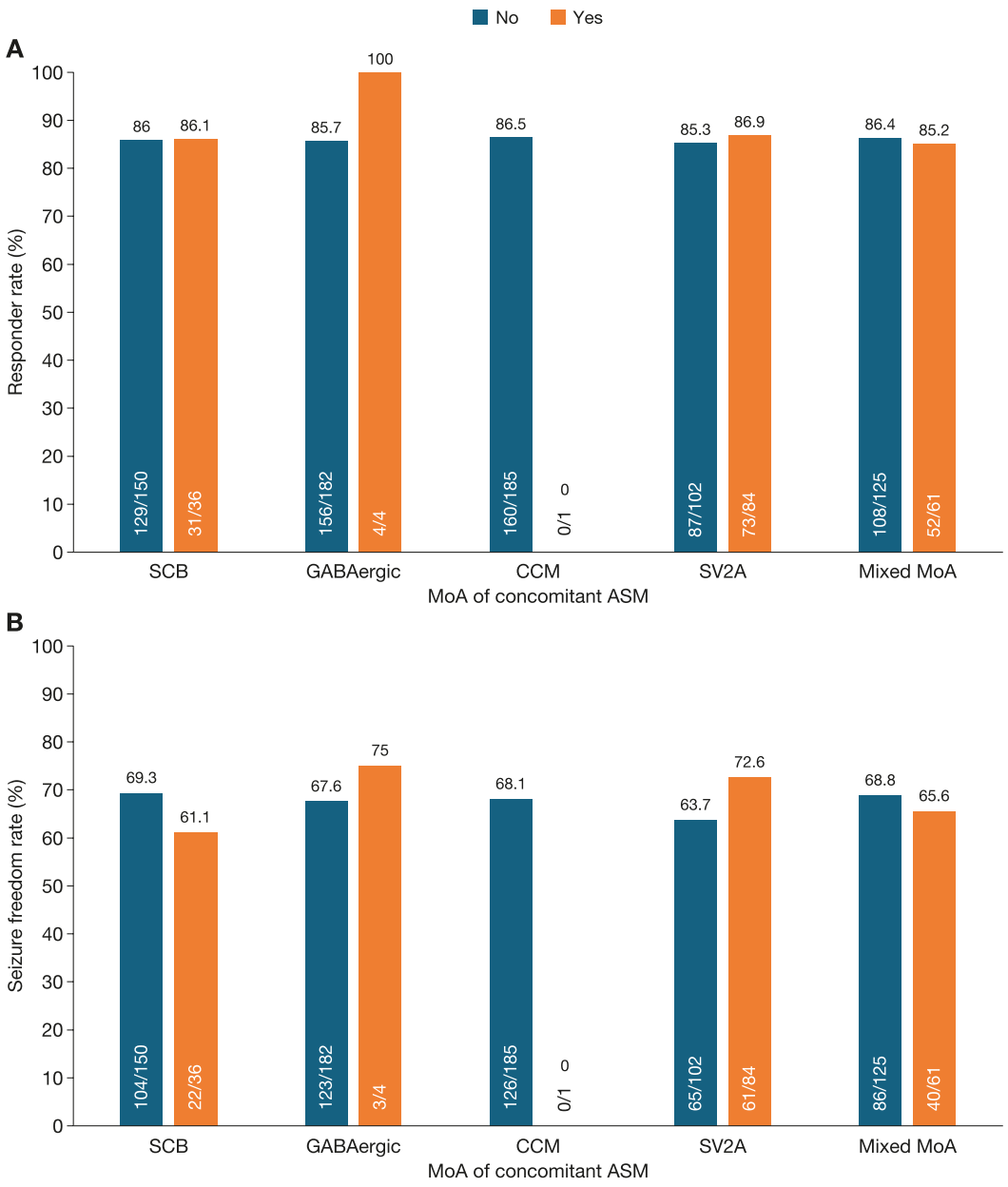

Fig. 5. Seizure frequency outcomes at the last visit in the subgroup with only generalised seizures and receiving only one concomitant ASM at baseline, according to the MoA of the concomitant ASM: (A) Responder rate and (B) Seizure freedom rate (Effectiveness Population). 'No' indicates 'not treated with concomitant ASM with specified MoA'. 'Yes' indicates 'treated with concomitant ASM with specified MoA'. ASM, antiseizure medication; CCM, calcium channel modulator; GABA, gamma-aminobutyric acid; MoA, mechanism of action; PER, perampanel; SCB, sodium channel blocker; SV2A, synaptic vesicle glycoprotein 2A.

significantly lower in individuals treated with versus without carbamazepine (48.5 % vs. 52.3 %; p = 0.049) and phenobarbital (45.7 % vs. 52.0 %; p = 0.030), and significantly higher in those treated with versus without clobazam (58.7 % vs. 50.2 %; p < 0.001), lacosamide (54.5 % vs. 50.5 %; p = 0.028), pregabalin (60.7 % vs. 51.1 %; p = 0.016) and primidone (63.0 % vs. 51.2 %; p = 0.046) (Fig. 8**A**).

In individuals with generalised seizures, there were no statistically significant differences in the occurrence of AEs according to the type of individual concomitant ASM (Fig. 8**B**).

3.4.4. Incidence of AEs according to the MoA of the concomitant ASM in individuals treated with only one concomitant ASM at baseline

There were no statistically significant differences in the occurrence of AEs according to the MoA of the concomitant ASM in individuals treated with only one concomitant ASM at baseline in participants with either focal seizures (Fig. 9**A**) or generalised seizures (Fig. 9**B**).

3.4.5. Incidence of AEs in individuals treated with EIASMs versus non-EIASMs

In individuals with focal seizures, there was no statistically significant difference in the incidence of AEs in those treated with concomitant EIASMs versus non-EIASMs (50.7 % [1052/2075] vs. 52.3 % [996/1905]), and the same was true for those with generalised seizures (47.8 % [65/136] vs. 49.4 % [315/638]).

3.4.6. Incidence of psychiatric AEs in individuals with versus without psychiatric comorbidity at baseline

In individuals with focal seizures, the incidence of psychiatric AEs was significantly higher in those with versus without psychiatric comorbidity at baseline (28.0 % [160/571] vs. 19.2 % [315/1644]; p <

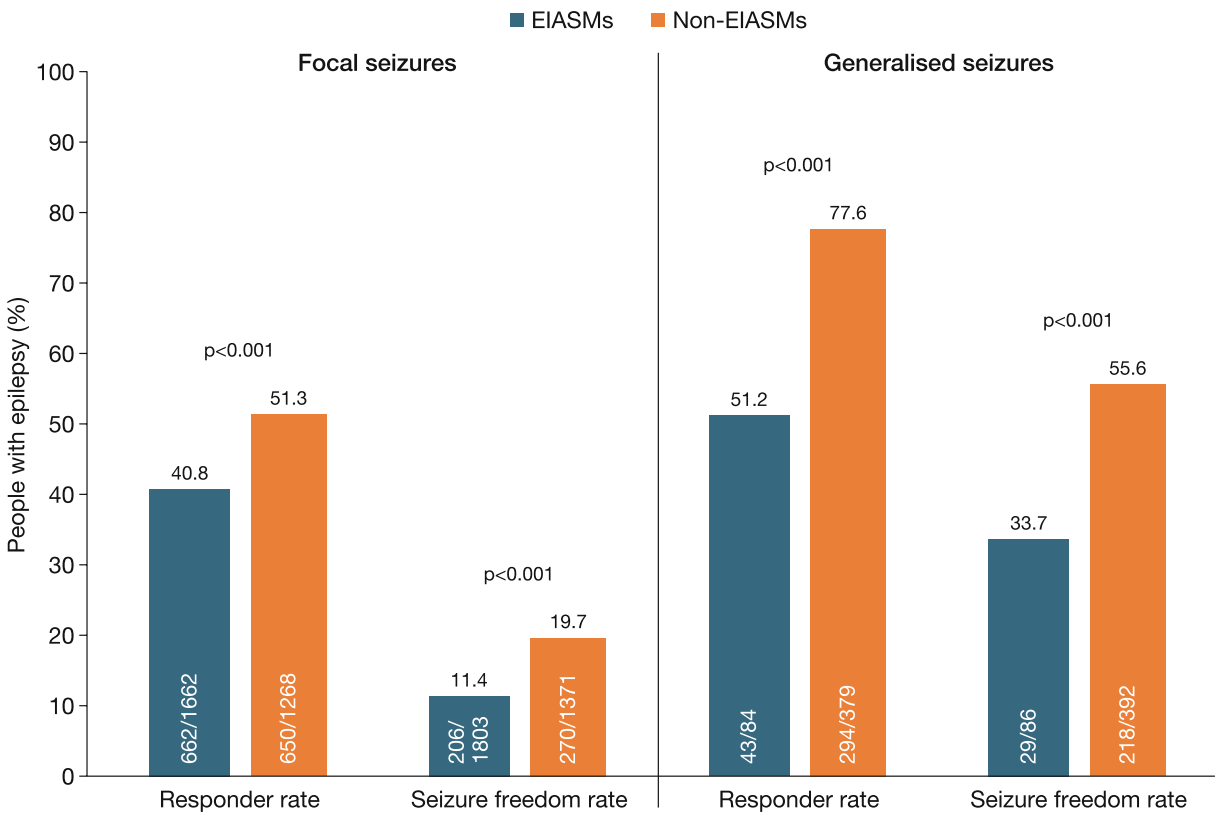

Fig. 6. Responder rate and seizure freedom rate at the last visit when PER was added to concomitant EIASMs versus non-EIASMs for the subgroups with only focal and only generalised seizures (Effectiveness Population). EIASM, enzyme-inducing antiseizure medication; PER, perampanel.

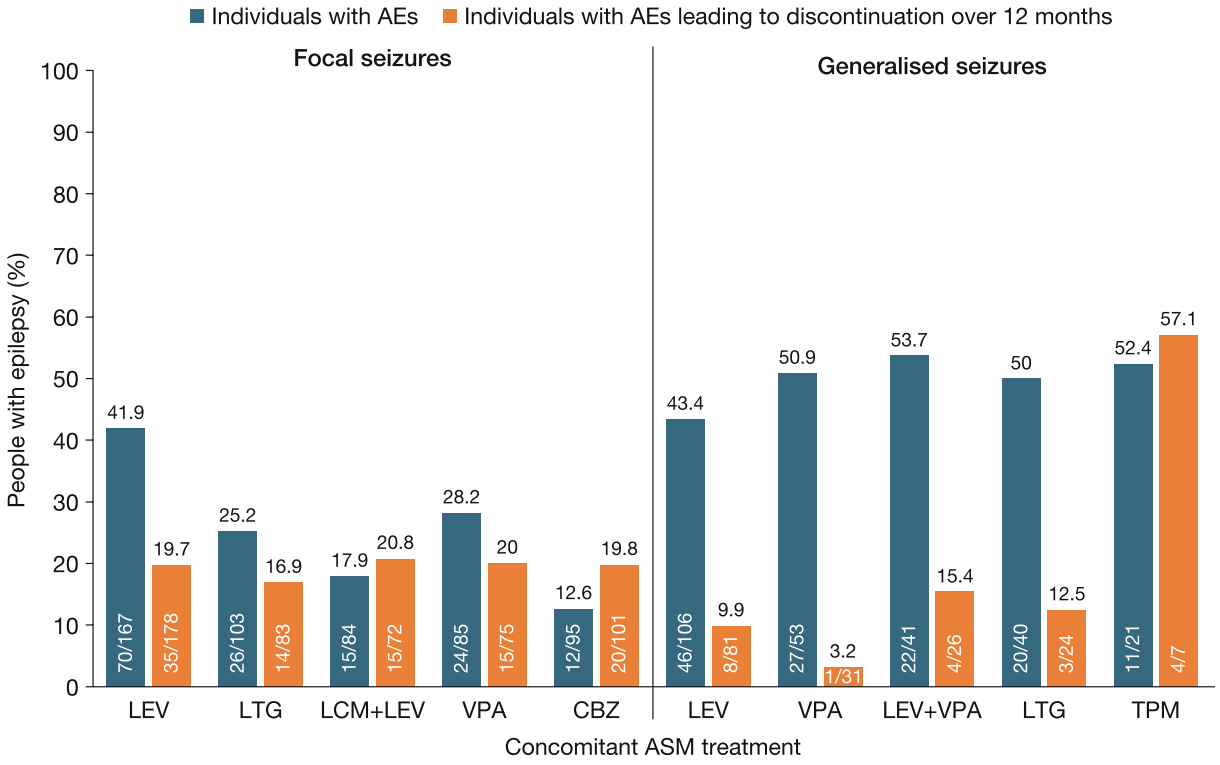

Fig. 7. Incidence of AEs and AEs leading to discontinuation over 12 months when PER was added to the top five most frequently used concomitant ASM treatments in the subgroups with only focal or only generalised seizures (Tolerability Population). AE, adverse event; ASM, antiseizure medication; CBZ, carbamazepine; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PER, perampanel; TPM; topiramate; VPA, valproate.

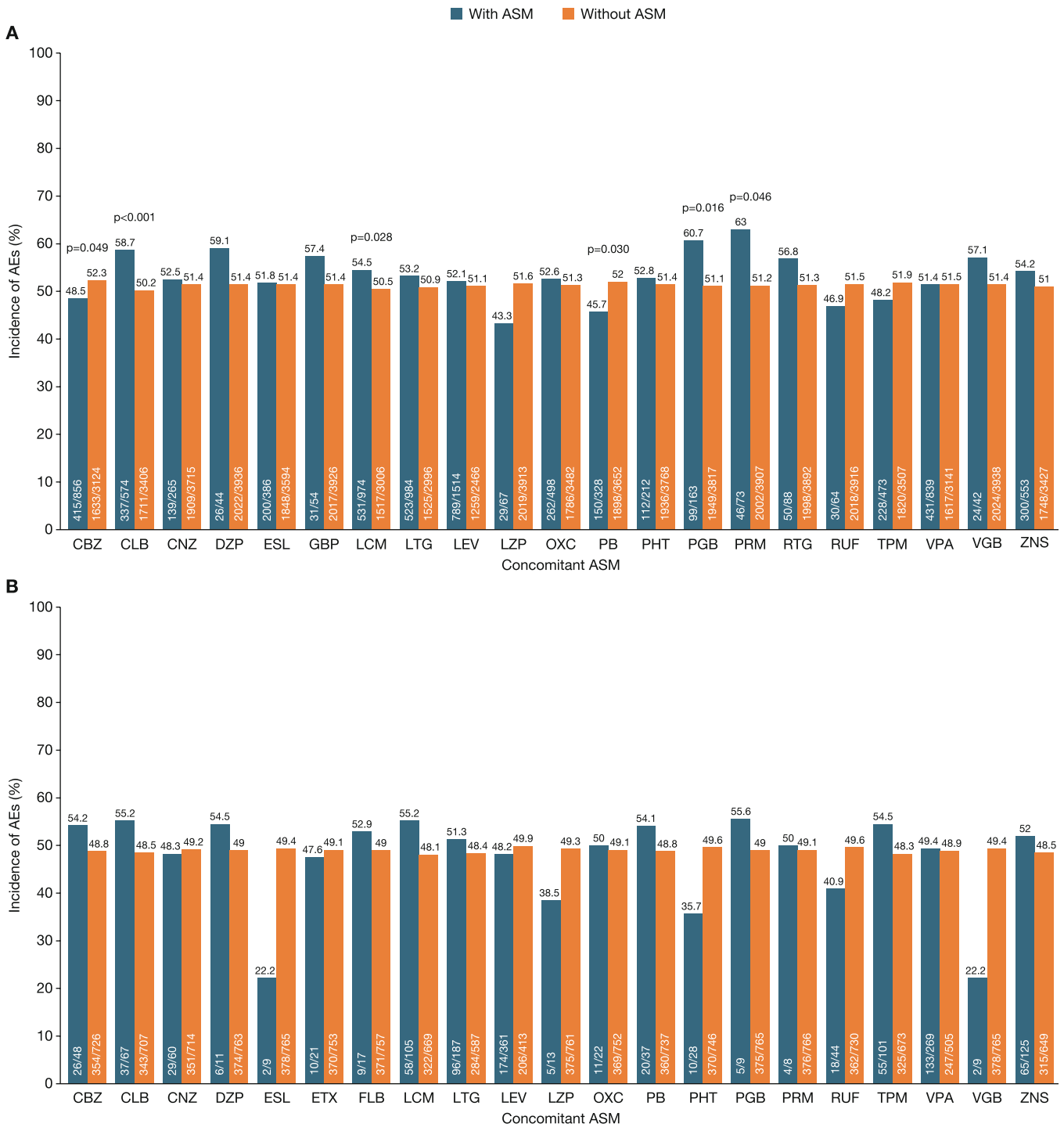

Fig. 8. Incidence of AEs during PER treatment according to the individual type of concomitant ASM in the subgroups with (A) Only focal seizures and (B) Only generalised seizures (Tolerability Population). Data are shown for concomitant ASMs used by ≥ 1 % of people with only focal seizures (N = 3980) and only generalised seizures (N = 774) at baseline. ASM, antiseizure medication; CBZ, carbamazepine; CLB, clobazam; CNZ, clonazepam; DZP, diazepam; ESL, eslicarbazepine acetate; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; LZP, lorazepam; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PGB, pregabalin; PHT, phenytoin; PRM, primidone; RTG, retigabine; RUF, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide.

0.001), and this was also the case for participants with generalised seizures (32.1 % [51/159] vs. 23.0 % [126/549]; p = 0.019).

3.4.7. Incidence of psychiatric AEs in individuals treated with versus without concomitant levetiracetam

There was no significant difference in the incidence of AEs in those treated with versus without concomitant levetiracetam in participants with focal seizures (20.2 % [304/1503] vs. 21.6 % [530/2456]) or generalised seizures (22.6 % [81/358] vs. 26.9 % [111/413]) (note: this analysis included individuals treated with other concomitant ASMs, not just levetiracetam).

4. Discussion

This *post-hoc* analysis of the PERMIT Extension study was carried out to provide real-world insights into the effectiveness and tolerability of

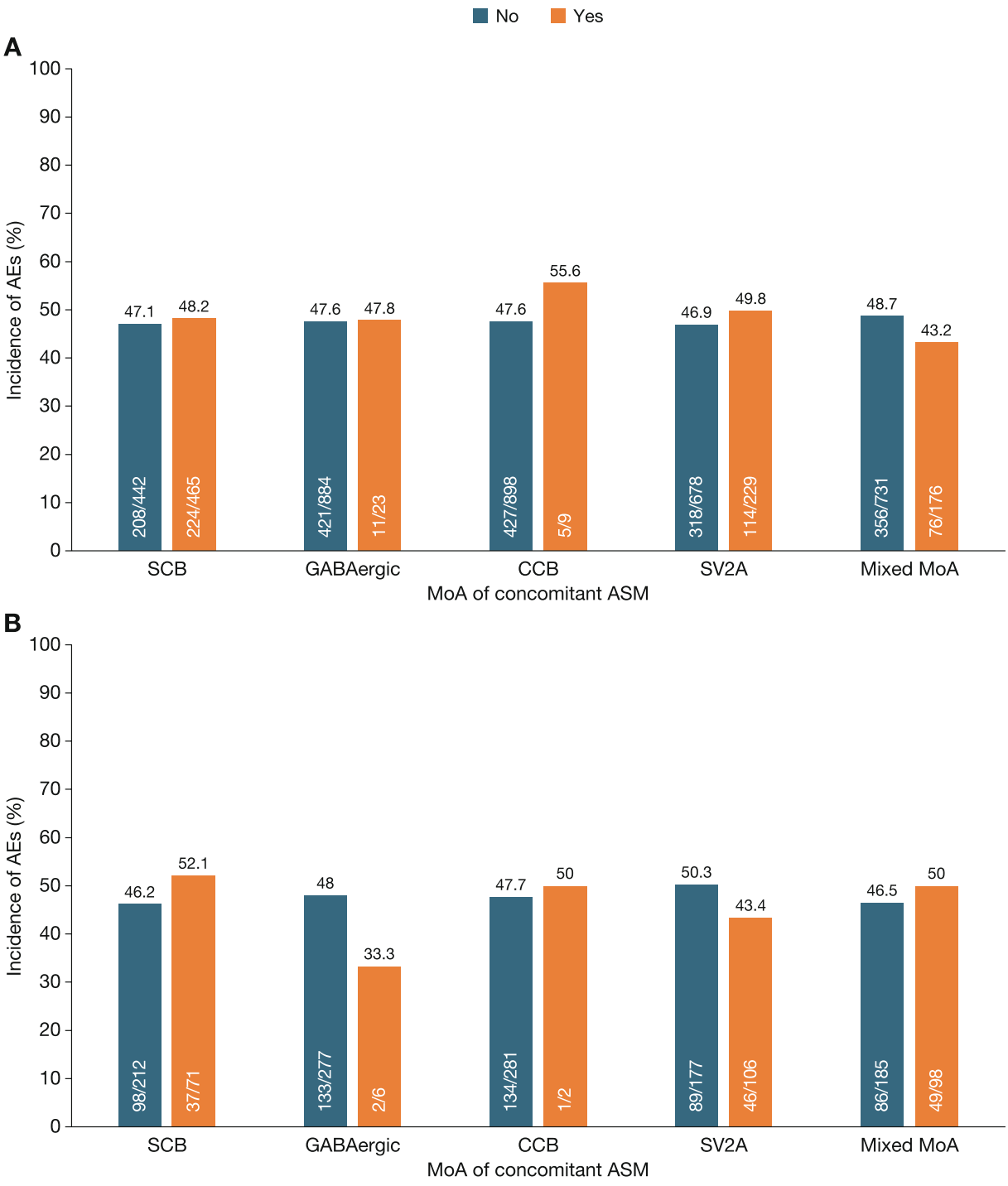

Fig. 9. Incidence of AEs during treatment with PER according to the MoA of the concomitant ASM in people receiving only one concomitant ASM at baseline in subgroups with (A) Only focal seizures and (B) Only generalised seizures (Tolerability Population). 'No' indicates 'not treated with concomitant ASM with specified MoA'. 'Yes' indicates 'treated with concomitant ASM with specified MoA'. ASM, antiseizure medication; CCM, calcium channel modulator; GABA, gamma-aminobutyric acid; MoA, mechanism of action; SCB, sodium channel blocker; SV2A, synaptic vesicle glycoprotein 2A.

PER when used in conjunction with a wide range of concomitant ASM regimens. As in the primary PERMIT Extension analysis [19], although PER was effective in individuals with only focal and only generalised seizures at baseline, it was particularly effective (in terms of responder and seizure freedom rates) in those with only generalised seizures. This may partly be accounted for by the fact that those with focal seizures, in comparison with those with generalised seizures, were older, had a longer duration of epilepsy, had been treated with more previous ASMs, and were being treated with more concomitant ASMs at baseline, indicating that the focal seizures subgroup was generally at a later disease stage and/or more refractory to treatment than the generalised seizures subgroup. Moreover, since there are more ASM options available for treating focal versus generalised seizures, it is possible that PER was chosen at a relatively late stage in those with focal seizures in the current study. As expected, the concomitant ASM regimens used to treat focal seizures differed from those used to treat generalised seizures; for example, the use of levetiracetam and valproate was less common in those with focal versus generalised seizures, while the use of lacosamide,

carbamazepine and oxcarbazepine was higher. Consistent with this, the use of EIASMs was higher in the focal versus generalised seizures subgroup, as was the use of SCBs and GABAergic ASMs, whereas the use of ASMs acting on SV2A and those with a mixed MoA was higher in the generalised versus focal seizures subgroup.

In the focal seizures subgroup, effectiveness varied considerably between the top five most commonly used concomitant ASM regimens, being most effective overall in the subgroup of individuals being treated with concomitant levetiracetam alone. In the generalised seizures subgroup, there was less variability in effectiveness across the top five most commonly used concomitant ASM regimens, with the exception of the subgroup treated with concomitant topiramate alone, which demonstrated the lowest responder and seizure freedom rates. Once again, effectiveness was most favourable in the subgroup of individuals with generalised seizures receiving concomitant levetiracetam alone. When seizure frequency outcomes were statistically compared for participants being treated with versus without individual ASMs, the concomitant use of valproate or diazepam was shown to significantly increase the responder rate in individuals with focal seizures, while the concomitant use of levetiracetam significantly increased the seizure freedom rate in this subgroup. Several concomitant ASMs significantly decreased effectiveness in the focal seizures subgroup, these tending to be those that are SCBs and/or EIASMs, such as carbamazepine, eslicarbazepine acetate, lamotrigine, lacosamide and phenobarbital, but also GABAergic ASMs, including clobazam and clonazepam; however, retigabine (a potassium channel-blocker) appeared to have the most detrimental impact on PER's effectiveness overall. Although it might not be surprising that the effectiveness of PER is reduced when given with concomitant EIASMs, it is interesting that its effectiveness varies with concomitant clobazam, clonazepam and diazepam. On the one hand, these drugs are benzodiazepines, which are characterised by the ability to increase GABA activity by binding to specific benzodiazepine-type receptors on the GABA-chloride ion channel complex [22]. Despite belonging to the same drug class, benzodiazepines differ in their therapeutic spectrum and activity, potency, and different pharmacokinetic properties, with differences being related to duration of action, depending on the metabolic half-life and active metabolite [22]. In addition, their MoA also presents variations: clobazam is a partial agonist to GABA receptors, while other benzodiazepines are typically full agonists [23]. On the other hand, it is possible that the baseline characteristics may have played a role in the different responses to the various benzodiazepines. Indeed, it is possible that patients receiving daily diazepam had worse seizure control at baseline, and that PER was more effective as an add-on in this subgroup than in the sub-groups of individuals receiving clobazam or clonazepam. Our findings highlight the need to consider several aspects of a drug's characteristics other than its MoA when combining ASMs, as well as patients' characteristics.

Consistent with these observations, the use of a concomitant SCB in individuals with focal seizures being treated with only one concomitant ASM at baseline significantly reduced PER's effectiveness, whereas the use of a concomitant ASM acting on SV2A (such as levetiracetam) significantly increased its effectiveness, as did the use of a concomitant ASM with a mixed MoA (in terms of responder rate, but not seizure freedom rate). However, it should be noted that the use of PER with concomitant levetiracetam in the subgroup with focal seizures was also associated with the highest percentage of patients experiencing AEs. Although the use of concomitant calcium channel modulators appeared to increase PER's effectiveness, the subgroup of individuals treated with calcium channel modulators was too small to ascertain statistical significance ($n = 5$). In individuals with generalised seizures, no individual concomitant ASM was associated with a significant increase in PER's effectiveness, but several ASMs were shown to significantly decrease its effectiveness. Once again, these tended to be SCBs, GABAergic ASMs and/or EIASMs, such as carbamazepine, clobazam, clonazepam, ethosuximide, lacosamide, lamotrigine, phenobarbital, and topiramate. In individuals with generalised seizures being treated with only one concomitant ASM at baseline, the MoA of the concomitant ASM did not significantly impact PER's effectiveness, although these observations may have been affected by small sample sizes. In individuals with focal seizures and in those with generalised seizures, the use of concomitant EIASMs significantly reduced PER's effectiveness, indicating that higher doses of PER may be required when used in conjunction with ASMs that are strong inducers of cytochrome P450 (CYP) enzymes such as CYP3A, consistent with PER's known pharmacological profile [11].

PER was generally well tolerated in individuals with focal seizures and in those with generalised seizures. In terms of the top five most commonly used concomitant ASM regimens, the incidence of AEs was highest in individuals with focal seizures treated with levetiracetam only, while in individuals with generalised seizures, the incidence of AEs leading to discontinuation was highest in those treated with topiramate only (although the size of this subgroup was small); in other respects, tolerability was similar across the commonest concomitant ASM regimen subgroups. When tolerability was statistically compared for participants being treated with versus without individual ASMs, the incidence of AEs was significantly lower in participants with focal seizures treated with versus without carbamazepine and phenobarbital, and significantly higher in those treated with versus without clobazam, lacosamide, pregabalin and primidone. In individuals with generalised seizures, no individual concomitant ASM was associated with a significant increase or decrease in the incidence of AEs. In individuals with focal seizures and in those with generalised seizures, there were no statistically significant differences in the incidence of AEs in terms of the MoA of the concomitant ASM in those treated with only one concomitant ASM, or in those treated with EIASMs versus non-EIASMs. In both the focal and generalised seizures subgroups, the incidence of psychiatric AEs was significantly higher in individuals with versus without pre-existing psychiatric comorbidity. However, it has previously been shown that a psychiatric history significantly increases the incidence of psychiatric AEs not only in individuals treated with PER but also in those treated with placebo [24]. Although psychiatric AEs are commonly associated with PER [11] and levetiracetam [25], in the current study the incidence of psychiatric AEs was not significantly higher in those treated with versus without levetiracetam, in both the focal and generalised seizures subgroups, consistent with previous reports [26–28].

Although the majority of individuals with epilepsy achieve seizure freedom with ASM monotherapy or the addition of one concomitant ASM, the likelihood of seizure freedom decreases with each successive ASM regimen [29] and most of those with refractory epilepsy are treated with two to four ASMs [3]. The increased likelihood of tolerability problems with ASM polytherapy, together with the decreased likelihood of achieving seizure freedom with each additional concomitant agent, has led to the concept of 'rational polytherapy' in order to optimise the likelihood of treatment success [3–7]. In clinical practice, implementation of rational polytherapy requires careful consideration of the pharmacological profiles of ASMs, in terms of both their potential for causing drug–drug interactions (e.g., through enzyme induction or inhibition) and their MoAs, since combining ASMs with different MoAs can potentially result in synergistic (supra-additive) effects [4]. The findings of the current study provide some confirmatory evidence to support this concept by demonstrating that the effectiveness of PER was affected by the MoAs of the ASM(s) to which it was added. In particular, the effectiveness of PER (a highly selective, noncompetitive AMPA receptor antagonist with broad-spectrum activity [8–10]) was increased when used in combination with an ASM that binds to SV2A (most commonly, levetiracetam). Although the increase in PER's effectiveness when used with levetiracetam was only statistically significant in the focal seizures subgroup, the increase was also evident in the generalised seizures subgroup, the smaller size of which may have precluded the detection of statistical significance. It is noteworthy that the use of levetiracetam alone was the most commonly used concomitant ASM regimen in both the focal and generalised seizures subgroups and encouraging that its use was not associated with a significant increase in psychiatric AEs. It is

also noteworthy and somewhat surprising that PER's effectiveness was enhanced when combined with levetiracetam, since both agents act on the excitatory side of seizure generation – something worthy of further investigation. Conversely, PER's effectiveness was significantly decreased when added to an SCB in the focal seizures subgroup, which may have reflected the enzyme-inducing effects of SCBs such as carbamazepine (which was used by 21 % of individuals in the focal seizures subgroup). The study's findings also support the concept of rational polytherapy in terms of the need to consider the pharmacological profiles of ASMs used in combination, since, in both the focal and generalised seizures subgroups, the use of EIASMs significantly reduced responder and seizure freedom rates in comparison with the use of non-EIASMs.

Despite the large size of the PERMIT Extension cohort, the study was limited in terms of sample size for some of the statistical comparisons conducted, particularly for the generalised seizures subgroup analyses. The ability to discern statistically significant differences in some of these analyses may also have been affected by the overall high responder and seizure freedom rates in the generalised seizures subgroup. Some individuals in the generalized seizures subgroup were treated with carbamazepine and oxcarbazepine (6.3 % and 2.8 %, respectively). Although these ASMs are not typically used to treat generalized seizures, they can be used to treat generalised tonic-clonic seizures; nevertheless, it is possible that the inappropriate use of these ASMs in some individuals may have affected outcomes. Differences in the baseline characteristics of the subgroups defined by concomitant ASMs might also have influenced the results; for example, it is possible that individuals treated with 'older' ASMs (i.e., ones that have been available for the longest time) had a longer duration of epilepsy, which might have impacted the effectiveness findings. Moreover, the concomitant drug regimen might have been changed over time and no data about concomitant ASMs at last follow-up visit were available. The study was also limited in being a *post-hoc* analysis of PERMIT Extension, which was itself a *post-hoc* analysis of previous clinical practice studies, the limitations of which have been discussed previously [19,20,30,31]. The results of this study should therefore be considered exploratory in nature.

In summary, this real-world study demonstrated that although PER was effective and generally well tolerated when used with a wide range of concomitant ASM regimens to treat individuals with focal and generalised seizures, there were important differences in outcomes depending on which concomitant regimen was used, which may help inform treatment decisions in the context of rational polytherapy.

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Data availability

Data will be made available on request.

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