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RESEARCH ARTICLE

Should substitution monotherapy or combination therapy be used after failure of the first antiseizure medication? Observations from a 30-year cohort study

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Abstract

Objectives: To assess the temporal trends in the use of second antiseizure (ASM) regimens and compare the efficacy of substitution monotherapy and combination therapy after failure of initial monotherapy in people with epilepsy.

Methods: This was a longitudinal observational cohort study conducted at the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland. We included patients who were newly treated for epilepsy with ASMs between July 1982, and October 2012. All patients were followed up for a minimum of 2 years. Seizure freedom was defined as no seizure for at least 1 year on unchanged medication at the last follow up.

Results: During the study period, 498 patients were treated with a second ASM regimen after failure of the initial ASM monotherapy, of whom 346 (69%) were prescribed combination therapy and 152 (31%) were given substitution monotherapy. The proportion of patients receiving second regimen as combination therapy increased during the study period from 46% in first epoch (1985–1994) to 78% in the last (2005–2015) (RR = 1.66, 95% CI: 1.17–2.36, corrected-p = .010). Overall, 21% (104/498) of the patients achieved seizure freedom on the second ASM regimen, which was less than half of the seizure-free rate on the initial ASM monotherapy (45%, $p < .001$). Patients who received substitution monotherapy had similar seizure-free rate compared with those who received combination therapy (RR = 1.17, 95% CI: 0.81–1.69, p = .41). Individual ASMs used, either alone or in combination, had similar efficacy. However, the subgroup analysis was limited by small sample sizes.

Significance: The choice of second regimen used based on clinical judgment was not associated with treatment outcome in patients whose initial monotherapy failed due to poor seizure control. Alternative approaches such as machine learning should be explored to aid individualized selection of the second ASM regimen.

KEYWORDS

add-on therapy, antiseizure medication, efficacy, second regimen

1 | INTRODUCTION

Antiseizure medications (ASM) are the mainstay of treatment for newly diagnosed epilepsy, the aim of which is to control seizures with minimal or no treatment related adverse effects. This is achievable in up to 70% of patients with appropriately chosen and trialed ASMs.[1] However, seizure freedom is not achieved on the first ASM monotherapy trial in more than half of the patients,[2] who require institution of a second ASM regimen. After failure of adequate trial of two appropriately chosen ASMs, the epilepsy is classified as 'drug resistant' prompting a different management path.[3] Therefore, it is important to choose the second regimen with great care.

Unlike for first ASM monotherapy,[4] there is limited high-level evidence to guide treatment decisions for the second ASM regimen after failure of initial monotherapy. It is uncertain whether the second ASM should substitute the first drug (substitution monotherapy) or be prescribed as an add-on (combination therapy) when the first ASM has failed solely due to inadequate seizure control.[5] A few observational studies have reported conflicting findings.[6–8] Two relatively small randomized clinical trials (RCTs)[9,10] found similar seizure-free rates between patients who received substitution monotherapy and combination therapy after the first ASM failed due to inadequate seizure control only. Many new ASMs with varied mechanism of actions and better tolerability profiles have become available over the last 30 years, exponentially increasing the choices for substitution or combination therapy. It remains to be seen how this has impacted treatment decisions and seizure outcomes on the second ASM regimen in clinical practice.

Using the extended Glasgow cohort, we analyzed the temporal trend of the use of substitution and combination therapies after failure of the initial ASM monotherapy over three decades. Further, we reported the treatment outcome on the second ASM regimen and compared the efficacy of each treatment strategy, individual ASMs and drug combinations used as second regimen and analyzed the risk factors associated with the seizure outcome.

Key points

- The proportion of patients receiving second regimen as combination therapy compared with substitution monotherapy increased over time
- The overall seizure-free rate on the second regimen reduced by more than half than the rate on the initial ASM monotherapy
- The seizure-free rate was similar regardless of the individual treatment strategy employed i.e., combination vs. substitution therapies
- Alternative approaches such as machine learning should be explored to aid individualized selection of the second ASM regimen

2 | METHODS

2.1 | Patients and setting

The study population consisted of 1795 people with newly diagnosed epilepsy and ASM regimen prescribed at the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland, between 1 July 1982 and 31 October 2012 as previously described.[2] For this analysis all individuals were followed up for a minimum of 2 years until 30 April 2016 or death. The study protocol was ruled exempt by the institutional review board of Western Infirmary, Glasgow.

2.2 | Treatment approach

As previously described,[2,6,11,12] initial ASM monotherapy was selected for a patient based on seizure type and other drug and personal factors.[13] Patients were reviewed every 2–6 weeks for the first 6 months after commencement of treatment, and thereafter every 4 months. Titration schedule[14] and doses were adjusted based on seizure control and emergence of adverse reactions, if any. At each clinic visit any adverse events (AEs) were recorded and their causal relationship with the ASM determined by the clinic physician, who documented whether drug withdrawal was due to intolerable adverse effects, poor seizure control or another reason. If patient was able to tolerate the initial monotherapy, had reduction in seizure frequency but failed to achieve complete seizure control, combination therapy was considered.[15] If the patient had intolerable AEs on the first ASM, a substitution ASM monotherapy was offered.

2.3 | Definitions

Response to ASM regimen was classified as success (absence of any type of seizures or auras for at least the preceding 12 months on unchanged medication); failure primarily due to poor seizure control only (did not achieve seizure freedom and no intolerable AE); and failure primarily due to poor tolerability only (reported intolerable AEs leading to withdrawal of the initial ASM). Other reasons unrelated to seizure control or tolerability such as planning a pregnancy and concern about teratogenicity were excluded from all analyses.

AEs were regarded as intolerable if they were stated as the main reason of discontinuation at the time of treatment failure. AEs were categorized according to Medical Dictionary for Regulatory Activities (MedDRA)[16,17] as previously described.[11]

The type of the second ASM regimen was classified as either substitution monotherapy or combination therapy. The ASMs prescribed that were developed before 1980 were considered as first-generation ASMs, and those introduced after were classified as second-generation ASMs (Table S1).[18] Individual ASM was also classified according to its purported mechanism of action and effect on the hepatic cytochrome P450 enzyme system. Drug load of ASM regimen was not included in the analysis as dosage was adjusted based on seizure control and tolerability, so patients who did not achieve seizure freedom would have been prescribed a higher dose if tolerated.

2.4 | Statistical analysis

The analysis cohort was defined as patients who were treated with second ASM regimen after the initial ASM monotherapy failed to provide adequate seizure control. Patients who had <1-year of follow-up on the second ASM regimen or with an undeterminable minimum 1-year treatment outcome (i.e., neither discontinued the treatment due to efficacy or tolerability reason, nor achieved 1-year seizure freedom) were excluded.

Continuous variables were expressed as medians and interquartile ranges due to non-normal distribution. Categorical variables were reported as frequency counts and percentages. Analysis was performed in patients who commenced the second ASM regimen. Given the diversity of ASM's mechanism of action and small numbers in some types, mechanism of action was dichotomised as sodium channel blocker and others in all the analyses. Univariable generalized linear model with Poisson distribution and robust error variance was used to screen potential risk factors associated with seizure freedom on the second ASM regimen after the first monotherapy failed due to poor seizure control. Variables with univariable p-value <.20 were selected for the multivariable analysis. Multivariable generalized linear model with Poisson distribution and robust error variance was used to estimate risk ratios (RRs) of seizure freedom. Pairwise comparisons of seizure-free rates between individual second ASM monotherapy were performed for ASMs used in at least 10 patients with adjustment of covariates included in the multivariable model. Seizure-free rates of individual second ASM combination therapies were descriptively summarized.

Level of statistical significance was set at $p < .05$. Holm-Bonferroni method[19] was used to correct for multiple comparisons in comparing treatment outcomes of ASM monotherapies. All statistical tests were performed by using Stata version 16.1 (StataCorp).

3 | RESULTS

Among the 1795 epilepsy patients in the original cohort, five discontinued their initial ASM monotherapy owing to planning a pregnancy and concern about teratogenicity, and were excluded from subsequent analyses. Of the remaining patients (n = 1790), 806 (45%) achieved seizure freedom on their initial ASM monotherapy, 745 (42%) did not become seizure free and 239 (13%) had poor tolerability.

3.1 | Second ASM regimen after the first ASM failed to control seizures

Of the 745 patients whose did not achieve seizure freedom on the initial treatment, treatment change was not observed in 246 (33%), and 499 (67%) commenced the second ASM regimen during the study period. One of these patients remained seizure-free on the second ASM but had <1-year follow-up, and was therefore excluded from analysis as the minimum 1-year treatment outcome could not be determined. The remaining 498 patients formed the analysis cohort, of which 346 (69%) were prescribed combination therapy and 152 (31%) were given substitution monotherapy (Figure 1). Table 1 summarizes the demographics and clinical characteristics of the analysis cohort. Demographics and clinical characteristics of the 246 patients who did not change treatment and excluded from the analysis are summarized in Table S2. The two groups had similar demographics and clinical characteristics.

3.2 | Trend of using substitution monotherapy and combination therapy

The proportion of second ASM regimen prescribed as combination therapy increased over the study period (Figure 2), from 46% (17/37) in 1985–1994 to 63% (122/195) in 1995–2004 and 78% (207/266) in 2005–2015. After adjusting for whether the patient reported any tolerability issue which was not the primary reason for treatment discontinuation on the initial ASM monotherapy, the proportion of combination therapy in the last epoch was still significantly higher compared to the first (RR = 1.66, 95%

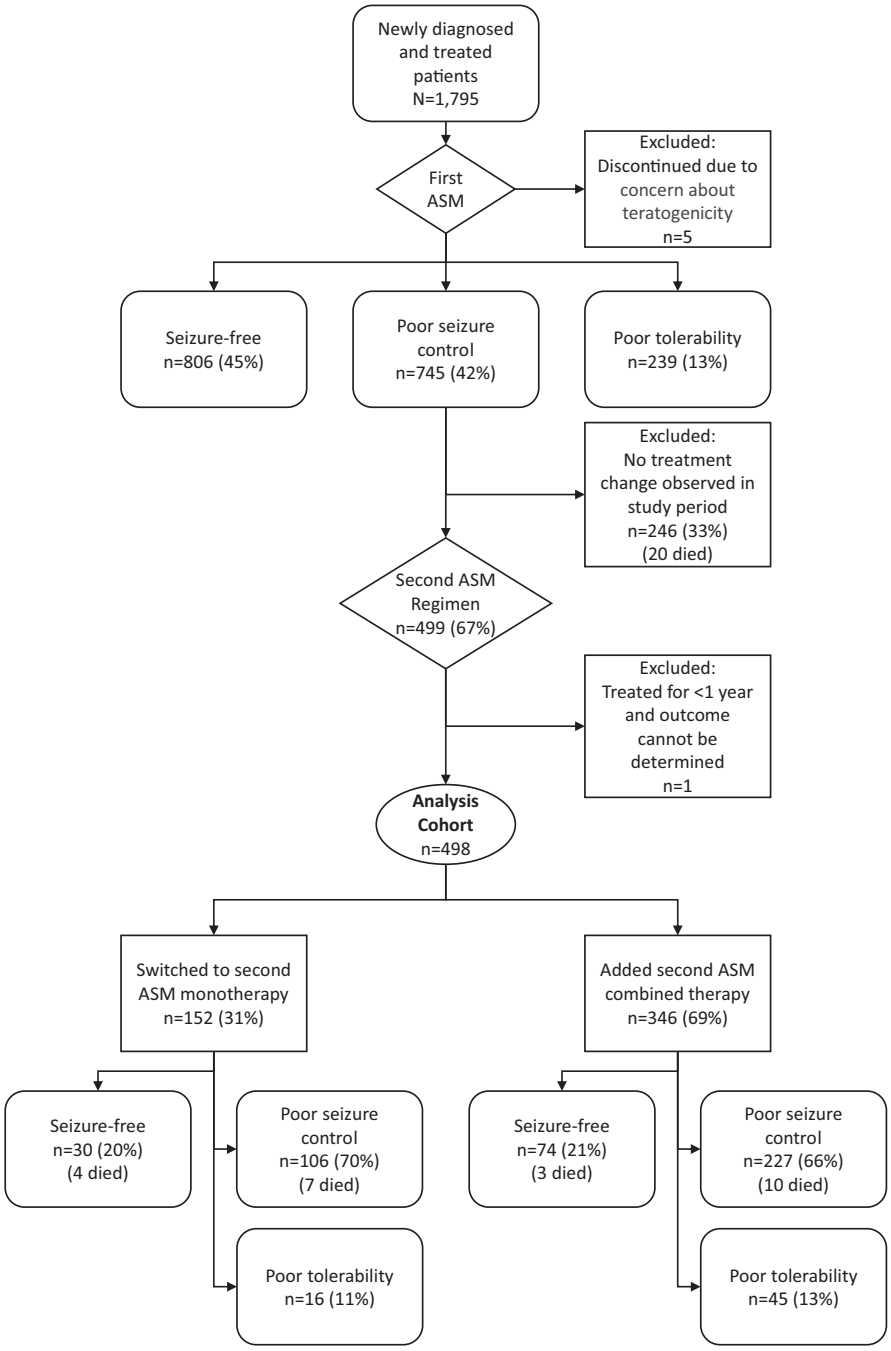

FIGURE 1 Flowchart of treatment outcome for the first two antiseizure medication regimens. Total percentage at individual level may be lower or higher than 100% due to rounding.

CI: 1.17–2.36, corrected-p = .010) and second (RR = 1.20, 95% CI: 1.07–1.36, corrected-p = .009), but there was no significant difference between the first and second epochs (RR = 1.38, 95% CI: 0.96–1.98, corrected-p = .079).

3.2.1 | Choice of substitution monotherapy

Valproate (n = 63, 41%), lamotrigine (n = 25, 16%) and carbamazepine (n = 24, 16%) were the most commonly used substitution monotherapy over the study period. However, the overall use of these ASMs as the second monotherapy gradually reduced over time while newer ASMs became available (Table S3). In terms of mechanism of action, ASMs with sodium channel blocking property were most commonly used (n = 65, 43%). Their proportion among the second ASM monotherapy was relatively stable over the three 10-year epochs (n = 10, 50%; n = 30, 41% and n = 25, 42%). As expected, patients who tried a sodium channel blocker as the initial monotherapy were more likely to switch to an ASM with different mechanism of action (RR = 1.72, 95% CI: 1.30–2.27, p < .001) after adjustments of treatment time epochs and whether the patient reported any tolerability issue on the first ASM.

TABLE 1 Demographics and clinical characteristics of the analysis cohort ($n = 498$).

Age at seizure onset – year, median (IQR)	28	(17–42)
Sex – Male (%)	273	(55)
Pretreatment seizure number (%)		
≤5	228	(46)
>5	270	(54)
Epilepsy type – *n* (%)		
Focal	392	(79)
Generalized	106	(21)
Epilepsy family history – *n* (%)	95	(19)
History of febrile seizure – *n* (%)	27	(5.4)
History of central nervous system infection – *n* (%)	8	(1.6)
History of birth trauma – *n* (%)	2	(0.4)
History of head injury – *n* (%)	88	(18)
History of cerebrovascular diseases – *n* (%)	57	(11)
History of psychiatric disorder – *n* (%)	183	(37)
History of learning disability – *n* (%)	23	(4.6)
History of drug misuse – *n* (%)	71	(14)
History of alcohol misuse – *n* (%)	121	(24)

Abbreviation: IQR, interquartile range.

3.2.2 | Choice of combination therapy

Lamotrigine was most frequently used as add-on ASM ($n = 91$, 26%), followed by levetiracetam ($n = 69$, 20%) and valproate ($n = 57$, 16%). Similar to trend observed in the substitution monotherapy, the overall proportion of lamotrigine and valproate used as add-on therapy gradually reduced over time. On the other hand, levetiracetam and lacosamide were increasingly used (Table S4). In terms of mechanisms of action of the combined drugs, a sodium channel blocker and an ASM with multiple mechanisms was the most common combination used ($n = 165$, 48%), followed by a sodium channel blocker and a synaptic vesicle protein 2A (SV2A) ligand, i.e., levetiracetam ($n = 81$, 23%), and a sodium channel blocker and a GABA analogue ($n = 35$, 10%). The choice of the add-on ASM was dependent on the mechanism of action of the initial monotherapy. It was more likely to add another ASM with different mechanism to an existing sodium channel blocker (RR = 3.38, 95%: 2.64–4.33, $p < .001$) after adjusted for treatment time epochs and whether the patient reported any tolerability issue on the first monotherapy.

Choice of ASMs used in the second regimen according to the epilepsy classification is provided in the supplement (Table S5).

3.3 | Response to substitution monotherapy vs. combination therapy

Overall, 21% (104/498) of the patients achieved seizure freedom on the second ASM regimen, which was less than half of the seizure-free rate on the initial ASM monotherapy (45%, $p < .001$). Similar seizure-free rates were observed in the 152 patients switched to substitution monotherapy ($n = 30$, 20%) and the 346 patients treated with combination therapy ($n = 74$, 21%, $p = .68$). Univariable screening showed treatment duration of the first ASM, time epochs at start of the second ASM regimen, pretreatment seizure number, epilepsy family history, history of cerebrovascular disease, history of psychiatric disorders, and history of drug misuse had $p < .20$ for association with seizure freedom on the second ASM regimen (Table S6). The seizure-free rates on the substitution monotherapy and combination therapy remained similar (RR = 1.17, 95% CI: 0.81–1.69, $p = .41$) after adjustments of these factors (Table 2).

3.3.1 | Response to substitution monotherapy

Valproate ($n = 63$, 41%), lamotrigine ($n = 25$, 16%), carbamazepine ($n = 24$, 16%) and levetiracetam ($n = 11$, 7.2%) were most commonly used substitution monotherapies in at least 10 patients. The seizure-free rates were not significantly different across these four ASMs (21% vs. 24% vs. 17% vs. 36%, respectively, $p = .60$). Responses to individual second ASM monotherapies are summarized in Table S7. There were also no significant differences in seizure-free rates between patients who tried second-generation ASM as the substitution monotherapy (13/63, 21%) and those who tried the first-generation ASM (17/89, 19%, $p = .82$), and between patients using sodium channel blockers (11/65, 17%) and ASMs with other mechanisms of action (19/87, 22%, $p = .45$).

Factors associated with response to substitution monotherapy

Univariable screening demonstrated the following clinically relevant variables had $p < .20$ for association with seizure freedom on the second ASM monotherapy (Table S8): generation of the first ASM, treatment duration of the first ASM, age at seizure onset, number of pretreatment seizures, family history of epilepsy, and history of cerebrovascular diseases. Including these factors in the multivariable analysis (Table 3), patients whose seizures were not initially controlled by a second-generation ASM had about half the chance to achieve

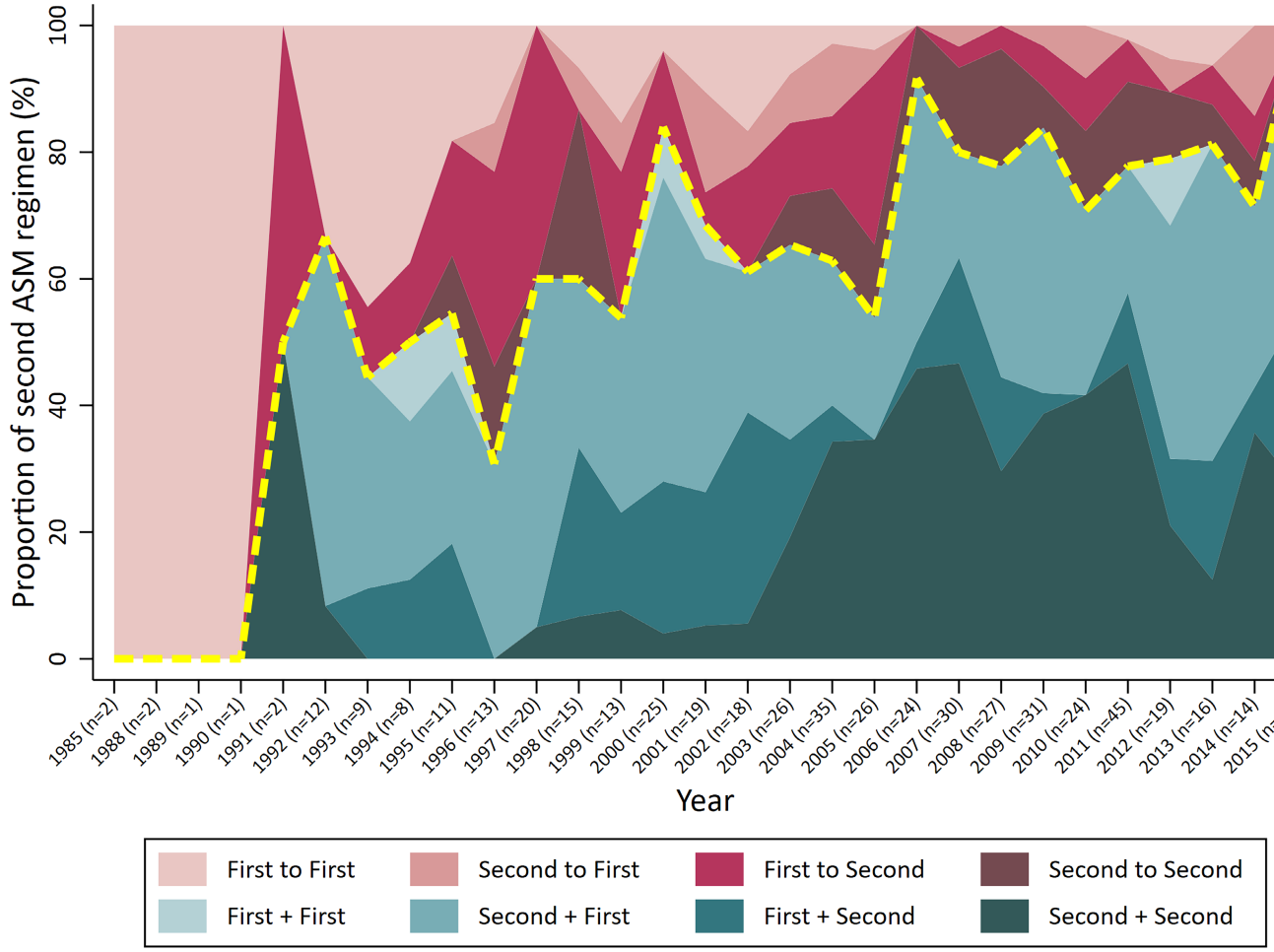

FIGURE 2 Trend of second antiseizure medication regimen use over the study period. The yellow dashed line divides the combination therapy in the bottom and the substitution monotherapy in the top. The areas in different shades of red indicate the proportions of different scenarios of substitution monotherapy (e.g., 'First to Second' indicates switching from a first-generation to a second-generation antiseizure medication). The areas in different shades of blue indicate the proportions of different combinations of combined therapy (e.g., 'First + Second' indicates adding a second-generation drug to the ongoing first-generation antiseizure medication treatment). The figure shows an increased trend of using combined therapy as the second regimen over the study period. The proportions of second-generation antiseizure medications used in the second regimen also increased over time.

seizure freedom on the second ASM monotherapy compared to those who initially tried a first-generation ASM (RR = 0.51, 95% CI: 0.27–0.94, $p = .032$). Family history of epilepsy was also associated with poor seizure control on the second ASM monotherapy (RR = 0.13, 95% CI: 0.02–0.89, $p = .037$). Patients with history of cerebrovascular disease, on the other hand, had more than 3 times the chance to become seizure-free on the second ASM monotherapy of those without history of cerebrovascular disease (RR = 3.32, 95% CI: 1.67–6.63, $p < .001$). However, further sensitivity analysis (Table S9) limited to ASMs used as the initial monotherapy in at least 20 patients, i.e., first-generation: valproate ($n = 29$), carbamazepine ($n = 27$); second-generation: lamotrigine ($n = 32$), levetiracetam ($n = 25$), did not show significant difference in achieving seizure freedom on the second ASM monotherapy (RR = 0.72, 95% CI: 0.38–1.33, $p = .29$).

3.3.2 | Response to combination therapy

Valproate and lamotrigine was the most frequently used combination in 113 patients (33%) followed by lamotrigine and levetiracetam in 44 patients (13%) and levetiracetam and valproate in 23 (6.6%). The seizure free rates were similar across individual ASM combinations used in at least 10 patients ($p = .61$). Combinations of ASM with different mechanism of actions, however, could have different seizure control effect. Responses to different second ASM add-on combinations are summarized in Table S10. The seizure-free rates of combination of sodium channel blocker and ASM with multiple actions (39/165, 24%) and combination of sodium channel blocker and SV2A ligand (23/81, 28%) were higher compared to pooled other combinations (12/100, 12%; corrected-$p = .040$; corrected-$p = .015$).

	RR	(95% CI)	*p*-Value	Corrected *p*-value[a]
Combination therapy vs. Monotherapy	1.17	(0.81–1.69)	.41	
Treatment duration of the first ASM – year	0.97	(0.91–1.03)	.36	
Time epochs at start of the second ASM			.12	
1995–2004 vs. 1985–1994	1.85	(0.80–4.29)	.15	.30
2005–2015 vs. 1985–1994	1.35	(0.58–3.14)	.49	.49
2005–2015 vs. 1995–2004	0.73	(0.51–1.04)	.077	.23
Pretreatment seizure number – >5 vs ≤5	0.75	(0.54–1.05)	.092	
Epilepsy family history – Yes vs. No	0.55	(0.30–0.98)	.042	
History of cerebrovascular diseases – Yes vs. No	1.49	(0.98–2.25)	.059	
History of psychiatric disorders – Yes vs. No	0.79	(0.54–1.16)	.24	
History of drug misuse – Yes vs. No	0.59	(0.29–1.19)	.13	

TABLE 2 Multivariable analysis of seizure freedom on the combination therapy vs. substitution monotherapy.

Abbreviations: ASM, antiseizure medication; CI, confidence interval; RR, risk ratio.

[a]Holm-Bonferroni method was used to correct for multiple comparisons.

	RR	95% CI	*p*-Value
Generation of the first ASM – Second vs. First	0.51	0.27–0.94	.032
Treatment duration of the first ASM – year	0.90	0.79–1.04	.16
Age at seizure onset	0.99	0.97–1.01	.46
Pretreatment seizure number – >5 vs. ≤5	0.72	0.40–1.30	.28
Epilepsy family history – Yes vs. No	0.13	0.02–0.89	.037
History of cerebrovascular diseases – Yes vs. No	3.32	1.67–6.63	<.001

TABLE 3 Multivariable analysis of associations between factors and seizure freedom on the second antiseizure medication monotherapy.

Abbreviations: ASM, antiseizure medication; CI, confidence interval; RR, risk ratio.

Factors associated with response to combination therapy

Combinations of ASM mechanism of action, treatment time epochs, epilepsy type, history of psychiatric disorders, and history of drug misuse had $p < .20$ in univariable screening (Table S11). Including these factors in the multivariable analysis (Table 4), only combination of sodium channel blocker and SV2A ligand (levetiracetam) had a better chance to achieve seizure freedom compared to the pooled other combinations (RR = 2.12, 95% CI: 1.11–4.03, $p = .023$) though it is not statistically significant after accounting for multiple comparison (corrected-$p = .69$). None of the other factors demonstrated independent association with seizure freedom on the combination therapy.

4 | DISCUSSION

More than half of the patients with newly diagnosed epilepsy in this cohort did not become seizure free on the initial ASM regimen. Of those patients who commenced a second ASM regimen after failure of the first regimen due to poor seizure control, combination therapy was increasingly favored over substitution monotherapy. The use of second-generation ASMs either alone or in combination increased in this cohort as they became available in clinical practice. However, the seizure free rates did not differ or improve over time regardless of the treatment strategy employed. The choice of individual ASM(s) used for substitution monotherapy, or in combination, did not affect the treatment outcome. Patients' seizures that were initially not controlled by a first-generation ASM monotherapy could have doubled the chance of achieving seizure freedom on subsequent substitution monotherapy, irrespective of the generation of ASM, compared to those who initially tried a second-generation ASM. No factors were identified as having an independent association with seizure freedom on combination therapy.

The overall seizure-free rate on the second ASM regimen was less than half of the rate on the first ASM. This outlook has not improved despite the introduction

TABLE 4 Multivariable analysis of associations between factors and seizure freedom on the second antiseizure medication combination therapy.

	RR	95% CI	*p*-Value	Corrected *p*-value[a]
ASM combinations			.074	
SCB + SV2A vs. SCB + Multiple mechanisms	1.23	0.78–1.92	.37	.37
SCB + SV2A vs. Other combinations	2.12	1.11–4.03	.023	.069
SCB + Multiple mechanisms vs. Other combinations	1.73	0.93–3.21	.086	.17
Time epochs at start of the second ASM			.13	
1995–2004 vs. 1985–1994	3.72	0.54–25.4	.181	.36
2005–2015 vs. 1985–1994	2.65	0.39–18.2	.322	.32
2005–2015 vs. 1995–2004	0.71	0.47–1.08	.107	.32
Epilepsy type – Focal vs. Generalized	0.84	0.54–1.32	.46	
History of psychiatric disorders – Yes vs. No	0.78	0.48–1.27	.32	
History of drug abuse – Yes vs. No	0.55	0.24–1.27	.16	

Abbreviations: ASM, antiseizure medication; CI, confidence interval; RR, risk ratio; SCB, sodium channel blocker; SV2A, synaptic vesicle protein 2A binding.

[a]Holm-Bonferroni method was used to correct for multiple comparisons.

of many new ASMs over time.[2] The underlying reasons are likely multifactorial,[20] but regardless, warrant a closer look to see if the available ASMs can be utilized better. After the failure of first regimen, the second ASM regimen can be trialed either as an alternate monotherapy (substitution therapy) or as add-on (combination therapy).[21] Substitution is the intuitive strategy when the first regimen is withdrawn because of poor tolerability. But the decision is not straightforward and evidence base guiding treatment strategy for further management is not robust when the first regimen requires change due to poor seizure control.[5,22,23] A study looking at commercial/Medicare database reported significant reduction in health care costs over 12-month follow up period in patients with drug resistant focal epilepsy on monotherapy after switching over to adjunctive (combination) therapy.[24] This study lacked the granular details to determine the actual reasons for drug changes in these patients. An observational study ($n = 596$) favored substitution over combination therapy with respect to efficacy in patients with focal epilepsy after failure of the initial regimen.[8] However, there the efficacy was similar in the subgroup analysis of patients whose initial monotherapy failed due to poor seizure control only. Our earlier study on the same cohort ($n = 248$) two decades ago revealed similar seizure free rates on substitution and combination therapies (17 vs. 26%) after failure of initial monotherapy due to poor seizure control only.[6]

A multicentre RCT in patients ($n = 157$) with focal epilepsy who had poor seizure control on previously trialed single or sequential monotherapies (i.e., not limited to first monotherapy) showed similar cumulative probability of remaining on the assigned treatment and seizure freedom at 1-year in the substitution and combination therapy groups, respectively.[9] The exact reasons for change in treatment at the time of randomization were not specified. Of note, 40% of patients had previously received more than one monotherapy, and thereby outcomes were not directly comparable to patients in whom only the first regimen has failed. In subgroup analysis of patients who had previously received a single monotherapy only, a non-significant trend towards higher retention rate was seen with add-on treatment. Power of this analysis was limited by small sample size. Similarly, another RCT in patients ($n = 264$) with focal epilepsy and poor seizure control on initial monotherapy did not favor either treatment strategy for further management in terms of efficacy and tolerability.[10] The clinical significance of these findings was limited by a short follow-up duration (6 months) and invalid determination of treatment outcome. Of note, both of these trials acknowledged not reaching half of the ideal sample size needed for the analysis because of logistical and feasibility concerns.[9,10] Our sample size of 498 patients exceeded both of these trials. Although we did not see difference in treatment outcomes between substitution or combination therapy at a group level, the sub group comparison of individual ASMs and combinations used was limited by small sample sizes. This underscores the difficulty in addressing this research question and calls for using alternate approaches.

A wide range of second-generation ASMs is now available enabling the clinicians to choose from drugs with improved pharmacokinetics, generally better tolerability and safety profiles.[20] Sodium channel blockers

were most commonly used monotherapy agents in our cohort. This could be reflective of predominance of patients with focal epilepsy (79%). Interestingly, family history of epilepsy and history of cerebrovascular disease were independent predictors of response to substitution monotherapy indicating that inherent pharmacoresistance or pharmacoresponsiveness is also driving the ultimate treatment response. Treatment failure on initial monotherapy with a second-generation ASM compared with a first-generation ASM cut down the chances of seizure freedom on the substitution monotherapy by half. The sensitivity analysis indicated that this difference was likely caused by some less commonly used second-generation ASMs. This could be reflective of a small sample size and warrants further investigation. Ever expanding treatment armamentarium has also enabled the clinicians to combine drugs with varied and synergistic mechanism of actions, potentially improving efficacy and minimizing additive toxicity.[20,25] This approach is supported by pre-clinical and clinical data.[22] A US claims database study reported longer persistence, and reduced rate of hospitalization and emergency room visits in patients with focal epilepsy using ASM combinations with varied mechanism of actions.[26] Most clinical evidence for an efficacious combination is available for sodium valproate and lamotrigine.[27,28] Other useful add-on therapies suggested in literature include phenobarbital with phenytoin for generalized tonic–clonic seizures,[29] valproate with ethosuximide for absence seizures,[30] vigabatrin with tiagabine for partial seizures,[31] carbamazepine with valproate or vigabatrin for partial seizures,[32] lamotrigine with topiramate for a range of seizure types,[33] and lamotrigine with levetiracetam.[34] However, there is paucity of well-designed randomized clinical trials. Sodium valproate and lamotrigine were the most frequently used drugs in combination in our cohort (33%), followed by lamotrigine and levetiracetam (13%). We did not see a significant difference in treatment outcome with any particular ASM combination though, including when grouped according to the mechanism of actions. This could be because of small sample size for most individual combinations used.

Machine learning techniques have demonstrated superior ability in unraveling non-linearities in data and identify relationships hidden from standard statistical methods.[35,36] According to SHAP analysis to ascertain the importance of clinical features in predicting the response of the first monotherapy trial, >5 pretreatment seizures, history of psychiatric disorders, and EEG and imaging findings were the most important determinants.[36] However, we did not find a significant association of these factors with the treatment outcome on second regimen in the current analysis, which may due to smaller sample size. Combining diverse cohorts[36] and using data augmentation techniques[37] for model training can potentially circumvent inherent limitations of dealing with small sample sizes. A recently developed deep learning model for predication of treatment response on initial ASM monotherapy in patients newly diagnosed with epilepsy has shown feasibility of an individualized treatment approach.[36] Similar models may be developed to guide treatment decisions for second ASM regimen in a personalized manner before a diagnosis of drug resistant epilepsy is made.

Despite reporting observations on a sizeable cohort collected during clinical practice over three decades, our study has limitations that warrant mention. The choice of using substitution or combination therapy was non-randomized in clinical practice. As the patients were recruited at a single site in Glasgow, there may be selection bias, and the results may not be generalisable to other populations. Disease and patient specific characteristics (e.g. etiology, genetic makeup etc.) may also impact treatment response. However, their effect could not be ascertained as relevant information was not collected in the study cohort. Using combination therapy may incur additional costs and a cost–benefit analysis would be useful. Although the information was collected during at each follow-up visit, introduction of information bias cannot be excluded. Lastly, only a few ASMs were frequently used either alone or in combination, which limits the statistical power of these analyses. The impact of newer ASMs as a second regimen in clinical practice remains to be seen.

5 | CONCLUSION

The proportion of second ASM regimen as combination therapy increased over time in this cohort. However, the seizure outcomes on substitution or combination therapy were similar, and type of ASMs used, either alone or in combination did not affect seizure outcome. However, the latter finding should be interpreted with caution and further studies with larger subgroup sample size are warranted. Machine learning approaches should be investigated in the future to guide personalized treatment choices after the first regimen fails.

AUTHOR CONTRIBUTIONS

Drs Kwan, Brodie and Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Brodie, Kwan, Chen, Hakeem. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Hakeem, Chen, Kwan. Critical revision of the manuscript for important intellectual content:

All authors. Statistical analysis: Chen. Administrative, technical, or material support: Brodie. Study supervision: Brodie, Kwan, Chen.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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