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Title Page

Title: Unanticipated improvement in seizure control in drug-resistant epilepsy- real world observations

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Highlights

- Drug-resistant epilepsy (DRE) occurs in a third of patients
- The value of serial anti-seizure medication (ASM) trials in DRE is controversial
- A retrospective study of unanticipated ASM responders in a DRE cohort
- Switching ASMs if no early response and rational polytherapy may improve outcomes

Abstract

Objectives

To determine the clinical features and anti-seizure medication (ASM) strategies associated with an unanticipated substantial improvement in seizure control in patients with drug-resistant epilepsy (DRE).

Methods:

This retrospective analysis of patients attending a tertiary care epilepsy clinic between 2008 and 2017 identified all patients with active DRE (at least 1 seizure per month for 6 months, despite treatment with 2 different ASMs). All treatment interventions were recorded from when DRE was first identified to the end of the study. The primary end points were seizure freedom or meaningful reduction in seizure frequency (greater than 75%) sustained for at least 12 months after a treatment intervention.

Results:

Three hundred and twenty-two patients were included in the analysis. Overall, 10% became seizure free following ASM adjustment and an additional 10% had a greater than 75% improvement in seizure control (median follow-up, 4 years). An ASM introduction was ten times more likely than an ASM dose increase to improve seizure control. Combined focal and generalized epilepsy, intellectual disability and prior treatment with more than 5 ASMs were more frequently observed in those with continued pharmacoresistance. ASM responders were more likely to have primary generalized epilepsy. Rational polytherapy (combining ASMs with different mechanisms of action) was almost ubiquitous amongst ASMs responders (95% taking at least 2 drugs with different mechanistic targets). Of the ASM additions that heralded improved seizure control, 85% were maintained at submaximal doses.

Conclusions:

This retrospective analysis of a large number of 'real-world' patients provides evidence to persist with ASM trials in DRE. Early rotation of ASMs if a clinical response is not observed at a substantial dose and rational ASM polytherapy may yield better clinical outcomes in patients with DRE, although a prospective study would need to be conducted to validate these findings.

Keywords:

Drug-resistant epilepsy; anti-seizure medication; unanticipated treatment response; rational polytherapy.

Introduction

Ultimately, more than one third of patients with epilepsy have seizures refractory to anti-seizure medications (ASMs), and the likelihood of treatment response diminishes exponentially with sequential unsuccessful medication trials.[1,2,3] These outcomes remain unchanged, despite the introduction of more than a dozen new ASMs in the past twenty years.[3] Accordingly, the International League Against Epilepsy (ILAE) defined drug-resistant epilepsy (DRE) as 'failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom'.[4]

Prospective data suggests that switching ASMs has little impact on seizure control and that changes in seizure frequency are due to spontaneous disease fluctuations.[5,6] These prospective studies were conducted on patients with infrequent seizures, treated with ASM monotherapy. As such, the applicability of these findings to DRE cohorts is questionable and these studies were limited by their small sample sizes.

Epilepsy surgery is four times more likely than medical therapy to achieve seizure freedom in DRE.[7] However, a substantial proportion of refractory patients are either ineligible for surgery, cannot access surgery or decline surgery. Additionally, approximately one third of patients have persistent seizures after epilepsy surgery.[8,9] Consequently, for a major proportion of patients with DRE, medications will remain the mainstay of treatment.

The reversibility of DRE without surgery has been infrequently studied. In a prospective study of incident childhood-onset DRE, over half the patients eventually became seizure free during 40-year median follow-up.[10] In adult DRE cohorts, 21-33% became seizure free for at least 12 months following medication adjustment.[11,12,13,14,15] These studies underscore the rationale to persist with ASM trials in apparently DRE. Rational polytherapy is often advocated in DRE but supporting clinical evidence is sparse and recommendations remain empirical.[16]

The aim of this study was to determine if unanticipated ASM responders had distinctive clinical characteristics when compared with persistent non-responders in a cohort of adult patients with heretofore DRE. The strategies and ASM regimens that led to a treatment response were analyzed to determine the value of serial ASM trials in DRE.

Methods

All patients with DRE attending a tertiary care epilepsy center between 2008 and 2017 were identified using a patient database. The epilepsy service has a track record of managing patients with DRE, many of whom were referred from other neurologists within the region for longitudinal care and consideration for epilepsy surgery. All patients were seen repeatedly by an epileptologist (D.J.C.) during that period. DRE was defined using the ILAE consensus statement.[4]

We included patients with active epilepsy (defined as at least one seizure per month over a minimum of six months), aged 16 years or older, on a fixed regimen of ASMs for at least six months prior to the study. They required follow-up in the clinic for at least 12 months after their last treatment adjustment. Patients with psychogenic non-epileptic seizures (PNES), evidence of poor treatment compliance and/or concomitant substance misuse were excluded to reduce the influence of confounding factors on treatment response. The diagnosis of epilepsy was made on the basis of detailed clinical assessment by the senior author (D.J.C.). In many patients ancillary evidence supportive of a DRE diagnosis was available, including routine electroencephalography (EEG) or video-EEG monitoring.

From a total database of 1865 patients attending the service between 2008 and 2017, 322 patients with DRE were identified and included in the analysis. Demographic and clinical features when they were first determined to be treatment resistant are shown in Table 1. The epilepsy type was classified according to the ILAE's most recent position paper.[17]

A pragmatic treatment strategy is used in the epilepsy clinic. ASMs are prescribed and adjusted by the consultant epileptologist (D.J.C.) until satisfactory seizure frequency is obtained. ASMs are titrated to a target dose rather than a target serum concentration, as therapeutic drug monitoring is not reliably

associated with improved clinical outcomes.[18,19] Tolerability is assessed by gradually titrating to an interim dose before increasing further to the target dose. The ASM is retained if it improves seizure frequency or severity. The duration of each trial varies depending on the baseline seizure frequency but in general there is early rotation of ASMs if they are deemed to be inefficacious. Polypharmacy (use of 3 or more ASMs) is avoided where possible, in an effort to minimize side effects. In those with highly active refractory epilepsy, abolition of convulsive or dangerous seizures is targeted, in an effort to reduce the risk of seizure-related injuries and sudden unexpected death in epilepsy (SUDEP).

We recorded all treatment interventions, from the date when DRE was first identified to the end of the study period. Treatment interventions included: drug introductions; drug withdrawals; dose increases; surgery; and vagal nerve stimulation (VNS). We classified a therapeutic intervention as a 'dose increase' when an ASM dose was increased after a period of 6 months or longer on a target dose.

Treatment response was ascertained from the patient's medical record and clinic letters. Generally, the baseline seizure frequency was recorded prior to a therapeutic intervention and the response documented in the follow-up clinic letter. If there was insufficient clinical information to accurately quantify seizure frequency following an intervention, the intervention was excluded from the analysis. The primary end points were seizure freedom or greater than 75% reduction in seizure frequency following a therapeutic intervention for at least 12 months. These high threshold endpoints in patients with a baseline seizure frequency of at least 1 seizure per month were chosen to avoid ambiguous treatment responses. Patients who reached the primary endpoints following drug interventions were categorized as 'ASM responders'.

Statistical analysis

Descriptive analysis of clinical characteristics was performed. All data were regarded as non-parametric and comparison between groups was by chi square test for categorical data and Mann-Whitney for continuous variables. Statistical significance was declared at a 0.05 significance level.

Standard protocol approvals, registrations, and patient consents

The data for this study were retrospectively collected and analyzed. The ethics committee of our institution approved this study, and considering the observational nature of the study, patient consent was waived.

Results

Amongst our cohort of 322 DRE patients, 626 ASM introductions, 194 ASM dose increases, 33 epilepsy surgeries and 11 VNS procedures were recorded. The response rates for each intervention are shown in Table 2. Epilepsy surgery was most likely to render patients seizure free at 12 months (15/33 or 45.45%), with an additional 10 epilepsy surgery patients experiencing a greater than 75% reduction (10/33 or 30.3%). Approximately 5% of individual ASM introductions were associated with seizure freedom at 12 months. The introduction of a new ASM was ten times more likely than an ASM dose increase to be associated with seizure freedom or a greater than 75% reduction in seizure frequency, 12 months after the intervention. A total of 66 patients (or 20.5% of the overall DRE cohort) had a greater than 75% reduction in seizure frequency one year after a medication intervention, of whom 50% (n=33) were seizure free. An additional 25 patients (or 7.76% of the overall DRE cohort) achieved this primary end point one year after epilepsy surgery. Twelve of the 25 (48%) epilepsy surgery responders had mesial temporal sclerosis.

Comparisons made between ASM responders and those who failed to experience meaningful seizure reductions are shown in Table 3. A greater proportion of ASM responders had primary generalized epilepsy compared with those who didn't respond (21.21% compared with 6.49%; p=0.0004). Twenty-eight of the 29 (96.55%) patients classified as having primary generalized epilepsy had seizures and interictal electroencephalographic discharges consistent with their diagnosis. No ASM responders with primary generalized epilepsy were treated with ASMs known to exacerbate generalized seizures, prior to their inclusion in the study (see Table 1 in supplementary materials). Of note, 2 patients with generalized epilepsy responded to a combination of levetiracetam and carbamazepine.

Non-responders were more likely to have combined generalized and focal epilepsy with multiple seizure types (22.94% compared with 1.52%; p=0.0001) and intellectual disability (57.14% compared with 33.33%; p=0.0014) (see Table 3). The percentage of patients with enduring pharmacoresistance was greater in those with prior treatment with ≥ 5 ASMs (57.14% compared with 33.33%; p=0.0007) or previous epilepsy surgery or VNS (18.18 % compared with 4.55%; p=0.0065). Age, gender, duration of epilepsy and baseline seizure frequency were similar between ASM responders and non-responders. There were no differences in the mean number of clinic visits and ASM changes per patient between the two groups. Nine deaths were recorded in the ASM non-responder group, of which 4 were directly attributable to poorly controlled epilepsy (3 SUDEP and 1 status epilepticus).

Within the ASM responder group, 33 (50%) were seizure free 12 months after a medication change, while the remaining patients had a greater than 75% reduction in seizure frequency 12 months after an intervention (see Table 2). Of note, 8 (12.12%) of these patients relapsed after a period of good seizure control. Within the ASM responder group 11 patients (16.67%) improved on ASM monotherapy. The remaining 55 patients (83.33%) responded to ASM combination therapy: 24 patients on 2 ASMs; 15 patients on 3 ASMs; and 16 patients on 4 ASMs (see Figure 1). The ASM introductions temporally related to treatment response are shown in Figure 2. In 56 cases (84.85%), the response was noted at submaximal daily doses.

The 10 most frequently added ASMs during the study period are shown in table 4. Lacosamide, perampanel, levetiracetam, zonisamide, and sodium valproate were the most frequently added ASMs. The mean and median daily dosages of the 10 most frequently prescribed ASMs were similar in both responders and non-responders. Certain ASMs, such as lamotrigine, phenytoin and topiramate were trialled more frequently prior to the study period (see Table 2 in supplementary materials).

Figure 1 demonstrates the ASM combinations, categorized by their presumed mechanism of action, used in those who became seizure free or who had a greater than 75% reduction in seizure frequency. Of note, 53 of the 55 (96.36%) combination therapy responders were taking at least 2 drugs from different mechanistic groups (40 patients on ASMs from 2 different classes; 16 patients on ASMs from 3 different classes; 5 patients on ASMs from 4 different classes). A sodium channel blocker (Na channel

blocker) and synaptic vesicle protein 2A modulator (SV2A modulator) combination was observed most frequently (n= 28); followed by a Na channel blocker and ASM with multiple pharmacological targets (multi-target ASM) combination (n= 22); followed by a combination of a SV2A modulator and a multi-target ASM (n= 15): followed by triple therapy with a Na channel blocker, a SV2A modulator and a multi-target ASM (n= 11); followed by a combination of a Na channel blocker and perampanel (n=9). Of the 11 patients who responded on monotherapy, 8 (72.73%) switched to an ASM with an alternative pharmacological target.

Discussion

In this study, we report a meaningful response to ASM therapy in a cohort of 'real world' patients with active DRE. Given the chronicity (median duration of epilepsy, 20.5 years; Table 1) and number of previously trialled ASMs (mean number of prior trialled ASMs, 5.2; Table 1), a poor overall prognosis would have been expected. Overall, 20% of patients achieved a meaningful improvement in seizure control one year after a medication adjustment, including 10% that resulted in seizure freedom. This and numerous other hospital-based [11,12,13,14,15] and long-term population-based[10] studies demonstrate that it is worthwhile persisting with ASM trials in those with apparently DRE. Epilepsy surgery was clearly the most efficacious treatment, as 45.45% of patients (15/33) became seizure-free after surgery and an additional 30.3% (10/33) had a greater than 75% reduction in seizures after surgery. However, epilepsy surgery reponders comprised of only 7.75% of our DRE cohort overall, highlighting the previously mentioned barriers to epilepsy surgery: patient eligibility, patient preference and availability.

Approximately 10% of all ASM introductions led to a meaningful treatment response of at least 75% seizure reduction. In contrast, only 1% of dose increases of an already-prescribed ASM led to improved seizure control (see Table 2). This concurs with our clinical experience, where if a substantial interim target ASM dose fails to produce an early clinical response, further dose increases rarely improve seizure control. This finding was observed in prospective studies where more patients became seizure free following ASM additions compared with dose increases.[5,6,12] Of note, we recorded more than three times as many ASM introductions compared with ASM dose increases, which may reflect biased practice at our epilepsy clinic. In our practice, serum ASM concentrations are not used routinely to guide dose titration. Instead, we monitor for a clinical response to a reasonable, submaximal dose of

the ASM. If a patient partially responded to an ASM, the dose was increased; if the ASM was ineffective at a submaximal dose, the ASM was usually withdrawn and another ASM trialled.

The factors found to be associated with enduring pharmacoresistance (see Table 3) were combined focal and generalized epilepsy, intellectual disability, prior treatment with at least five ASMs and prior failed epilepsy surgery or active VNS therapy. ASM responders were more likely to have primary generalized epilepsy. These findings were in agreement with previous studies that found an association between pharmacoresistance and intellectual disability[10,12,13,20] and the number of previously trialled ASMs.[1,2,3,11,12,13,21] Prior studies indentified an associated between primary generalized epilepsy and favorable treatment responses in apparently DRE.[11,22] Combined focal and generalized epilepsy was included as a new category in the latest iteration of the ILAE classification of the epilepsies,[17] and as this category includes severe forms of epilepsy, including the epileptic encephalopathies, it unsurprisingly was associated with enduring pharmacoresistance. Numerous studies[11,12,13] identified duration of intractability as a predictor of persistent refractory epilepsy, whereas in our cohort, duration of epilepsy was similar in ASM responders and non-responders. A similar finding was observed in a prospective cohort, where duration of pre-existing seizure freedom had no bearing on the likelihood of remaining seizure free after switching ASMs.[5]

Our analysis of the ASM regimens used in those who experienced an apparent response yielded a number of observations. Approximately two thirds of the ASM additions temporally related to improved seizure control were agents licensed in the past two decades (lacosamide n=13; levetiracetam n=11; perampanel n=9; zonisamide n=7; eslicarbazepine n=4; brivarecetam n=1; Figure 2). Of the ASM additions that heralded reduced seizure frequency, almost 85% were maintained at submaximal daily doses. This supports pre-existing data, which demonstrated that patients who became seizure free on ASMs, did so on modest to moderate doses in most cases.[23] Rational polytherapy was almost ubiquitous amongst ASMs responders, whether coincidental or otherwise. Over 95% of those who experienced significantly improved seizure control on combination therapy were taking at least 2 drugs with different mechanisms of action (see Figure 1). Combinations of sodium channel blockers with SV2A modulators, multi-target ASMs or perampanel were observed in over two thirds of responders. In addition, most ASM monotherapy responders had switched to an agent with a different mechanism of action.

Approximately an eighth of ASM responders relapsed during the study period. In a prospective cohort study, almost 60% of patients relapsed after becoming seizure free for one year (5.9 years median follow-up).[13] An unpredictable relapsing-remitting pattern of seizure frequency is seen in 16%-52.2% of patients with epilepsy.[2,22] In patients with this epilepsy trajectory, periods of seizure freedom may be part of the natural history of the disease and it is debatable whether ASM manipulation prompts remission. It is estimated that among adult DRE patients, 5% per year enter seizure remission, irrespective of ASM changes.[12,13]

We categorized a greater than 75% reduction in seizure frequency 12 months after a treatment intervention as a meaningful outcome, as we felt it captured a cohort with significantly reduced convulsive seizures, status epilepticus, injuries, hospitalizations and deaths. DRE is defined as failure to induce seizure freedom with ASMs and this is reflected in epilepsy research, where outcomes are typically dichotomized into absolute seizure freedom or not. [1,2,3,5,6,10,12,13,15] In surgically treated epilepsy patients, seizure freedom is the only outcome measure associated with improved quality of life.[24,25] This has been indirectly demonstrated in two small studies of patients treated with ASMs only, where driving was the only outcome associated with improved quality of life (in most jurisdictions, driving is restricted until a person is 1 year seizure free).[26,27] Severe, potentially injurious seizures contribute to anxiety and socially-avoidant behaviour, and are associated with reduced quality of life measures independent of seizure frequency.[28,29] Infrequent convulsive seizures are a desirable outcome in DRE as it reduces the risk of SUDEP and death from status epilepticus. Uncontrolled epilepsy is associated with a significant mortality rate, demonstrated by the 4 epilepsy-related deaths in the non-responder group.

A number of study limitations warrant mentioning. First, as a retrospective observational study the treatments were neither randomized nor blinded, introducing bias to the outcome evaluations and making inferences of causality difficult. Furthermore, the retrospective design meant that important data were not always available. Indeed, there was no standardized format of recording seizure frequency in the medical record and we relied on patient reports of seizure frequency, which may underestimate the true frequency. Second, as patients were typically treated with combinations of ASMs, attributing a clinical response to an individual intervention was challenging. In an effort to differentiate the contribution of established ASM regimens from recent ASM additions, we only included patients on a

fixed regimen of ASMs for at least six months prior to the study. Third, serum ASM levels were not routinely used to guide dosage adjustments. Prospective studies have failed to show that serum ASM concentrations relaibly correlate with ASM responsiveness[18,19] and the doses reached in the present study were comparable to a treatment protocol utilized in an observational DRE treatment study.[11] Fourth, the senior author's (D.J.C.) preference for rapid cycling of ASMs if an early response is not obtained may not be representative of current practice. Fifth, factors associated with 'pseudoresistance', including poor compliance, substance misuse, inappropriate ASM prescribing for seizure type or suboptimal dosing may have been responsible for apparent ASM resistance.[30] Indeed, in some cases PNES rather than epileptic seizures may have accounted for the main burden of disease. We excluded patients with a known history of PNES, substance misuse or nonadherence to ASMs, in an effort to control for these confounding factors.

The 'real world' orientation of the study meant patients had heterogeneous treatment regimens, including combinations of ASMs that were introduced and withdrawn at varied points in time, epilepsy surgery and VNS. As most patients with DRE take multiple ASMs, prospective drug trials are challenging and the prospective ASM switching studies have questionable applicability to DRE, as they were conducted on patients with infrequent seizures, treated with ASM monotherapy.[5,6] In the present study, the retrospective design and heterogeneity of treatments recorded limit the conclusions that can be drawn from individual interventions. Notwithstanding these limitations, our findings point towards a benefit in DRE with early ASM switching, if an improvement is not noted after a reasonable trial, on a modest dose. While, the long-term outcomes in epilepsy have remained largely unchanged despite the introduction of many new ASMs,[3] it is plausible that certain combinations of ASMs may be more efficacious than others and the improved tolerability of newer agents may facilitate rational polytherapy.[31] Beyond the well described therapeutic synergism between lamotrigine and sodium valproate, the literature supporting rational polytherapy is sparse.[16] Isobolographic analysis[32,33] and post-hoc analyses of lacosamide clinical trial data[34] suggest that certain ASM combinations may have synergistic interactions. In the present study, responders were treated with combinations of ASMs with different mechanisms at submaximal daily doses.

In conclusion, one fifth of our apparently DRE cohort experienced improved seizure control following ASM adjustment. Combined focal and generalized epilepsy, intellectual disability and prior treatment with more than five ASMs were more frequently observed in those with continued pharmacoresistance. Responders were more likely to have primary generalized epilepsy and to respond to a trial of a new ASM rather than adjustment in the dose of an existing ASM. The application of a systematic treatment protocol, where combinations of ASMs with different mechanistic targets are trialled and rotated early if a clinical response is not observed at a substantial target dose may yield better outcomes in chronic refractory epilepsy but this hypothesis warrants further investigation, ideally by prospective analysis. The deaths attributable to epilepsy highlight the significant consequences of uncontrolled epilepsy and that perseverance with ASM trials may be worthwhile to achieve palliative goals, such as reducing convulsive seizures or preventing status epilepticus.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Baseline Patient Characteristics

Characteristics	***n= 322***
Mean age (range), year	34.7 (16-70)
Male (%)	176 (54.7)
Duration of epilepsy, years[a]	
Mean	23.3
Median	20.5
Range	3-64
Epilepsy classification[b]	
Focal (%)	169 (52.5)
Generalized (%)	29 (9)
Combined (%)	54 (16.8)
Unknown (%)	70 (21.7)
Intellectual Disability (%)	157 (48.8)

Number of prior ASMs		
	Mean	5.2
	Median	5
	Range	2-18
Prior surgery (%)		12 (3.7)
Prior VNS (%)		36 (11.2)
Seizure frequency, per month		
	1-5 (%)	151 (46.9)
	6-10 (%)	85 (26.4)
	>10 (%)	86 (26.7)
Duration of follow-up in study, year		
	Mean	4.5
	Median	4
	Range	1-8

a. In 13 patients, the exact duration of epilepsy was not known and was reported as 'longstanding' or 'childhood epilepsy.'
b. Epilepsy classified using the ILAE 2017 position paper.[17]

Table 2: Clinical response to therapeutic interventions

Therapeutic Intervention	**New ASM**	**Dose Increase**	**Surgery**	**VNS**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Number of interventions	626	194	33	11
Seizure free 1 year after intervention	33 (5.27)	0 (0)	15 (45.45)	0 (0)
>75% seizure reduction 1 year after intervention, including those seizure free	64 (10.22)	2 (1.03)	25 (75.76)	0 (0)

Table 3: Comparative analysis of patients who experienced meaningful improved seizure control and those who remained drug resistant

Characteristics	**ASM responders** *n= 66*	**ASM non-responders** *n= 231*	***P***
Baseline characteristics			
Mean age (SD), years	34 (13.38)	35.14 (13.91)	0.5542
Male, (%)	35 (53.03)	131 (56.71)	0.5960
Duration of epilepsy ≥ 10 years (%)[a]	52 (78.79)	190 (82.25)	0.5241
Epilepsy classification[b]			
Focal (%)	37 (56.06)	107 (46.32)	0.1633
Generalized (%)	14 (21.21)	15 (6.49)	**0.0004**
Combined (%)	1 (1.52)	53 (22.94)	**0.0001**
Unknown (%)	14 (21.21)	56 (24.24)	0.6096
Intellectual Disability (%)	23 (34.85)	132 (57.14)	**0.0014**

≥ 5 ASMs previously taken (%)	22 (33.33)	132 (57.14)	**0.0007**
Prior surgery/VNS (%)	3 (4.55)	42 (18.18)	**0.0065**
Seizure frequency, per month			
1-5 (%)	31 (46.97)	112 (48.48)	0.8289
6-10 (%)	17 (25.76)	61 (26.4)	0.9171
>10 (%)	18 (27.27)	53 (25.1)	0.7220
Interventions during study period			
Mean number of clinic visits (SD)	9.38 (4.56)	9.87 (6.09)	0.5446
Mean ASM changes per patient (SD)	1.83 (1.37)	1.90 (1.80)	0.7701
Mean ASM dose increases per patient (SD)	0.52 (0.64)	0.60 (0.68)	0.3940
Outcomes			
Death (%)	0 (0)	9 (3.90)	-

a. In 13 patients where duration of epilepsy was reported as 'longstanding' or 'childhood epilepsy', duration was categorized as greater than or equal to 10 years.
b. Epilepsy classified using the ILAE 2017 position paper.[15]

Table 4: 10 most frequently added ASMs in patients who experienced meaningful improved seizure control and those who remained drug resistant

	ASM Responders			**ASM Non-responders**		
	ASM added during the study period (%)	*Median daily dose (mg)*	*Mean daily dose (mg)*	*ASM added during the study period (%)*	*Median daily dose (mg)*	*Mean daily dose (mg)*
LAC	28 (42.4)	350	336.36	86 (37.2)	300	323.38
PER	13 (19.7)	6	7.5	64 (27.7)	6	5.79
LEV	22 (33.33)	2000	2347.22	39 (16.9)	2000	2219.29
ZNS	14 (21.2)	400	370.83	34 (14.7)	300	320.36

VLP	9 (13.6)	1400	1476	31 (13.4)	1500	1459.83
CLB	4 (6.1)	15	16.25	30 (13)	20	20
CBZ	8 (12.1)	700	895.24	25 (10.8)	800	804.87
LTG	7 (10.6)	325	386.66	23 (10)	350	333.94
ESL	6 (9.1)	800	950	23 (10)	800	953.33
BRIV	2 (3)	150	150	26 (11.3)	175	171.15

Abbreviations used in table 4:

VPA= valproic acid; TPM= topiramate; ZNS= zonisamide; RUF= rufinamide; CBZ= carbamazepine; PHT= Phenytoin; LTG= lamotrigine; OXC= oxcarbazepine; ESL= eslicarbazepine; LAC= lacosamide; LEV= levetiracetam; BRV= brivarecetam; PB= phenobarbital; CLB= clobazam; PER= perampanel

Figure titles and legends

Figure 1 title:

ASM combinations categorized by their presumed mechanism of action in those who experienced meaningful improved seizure control

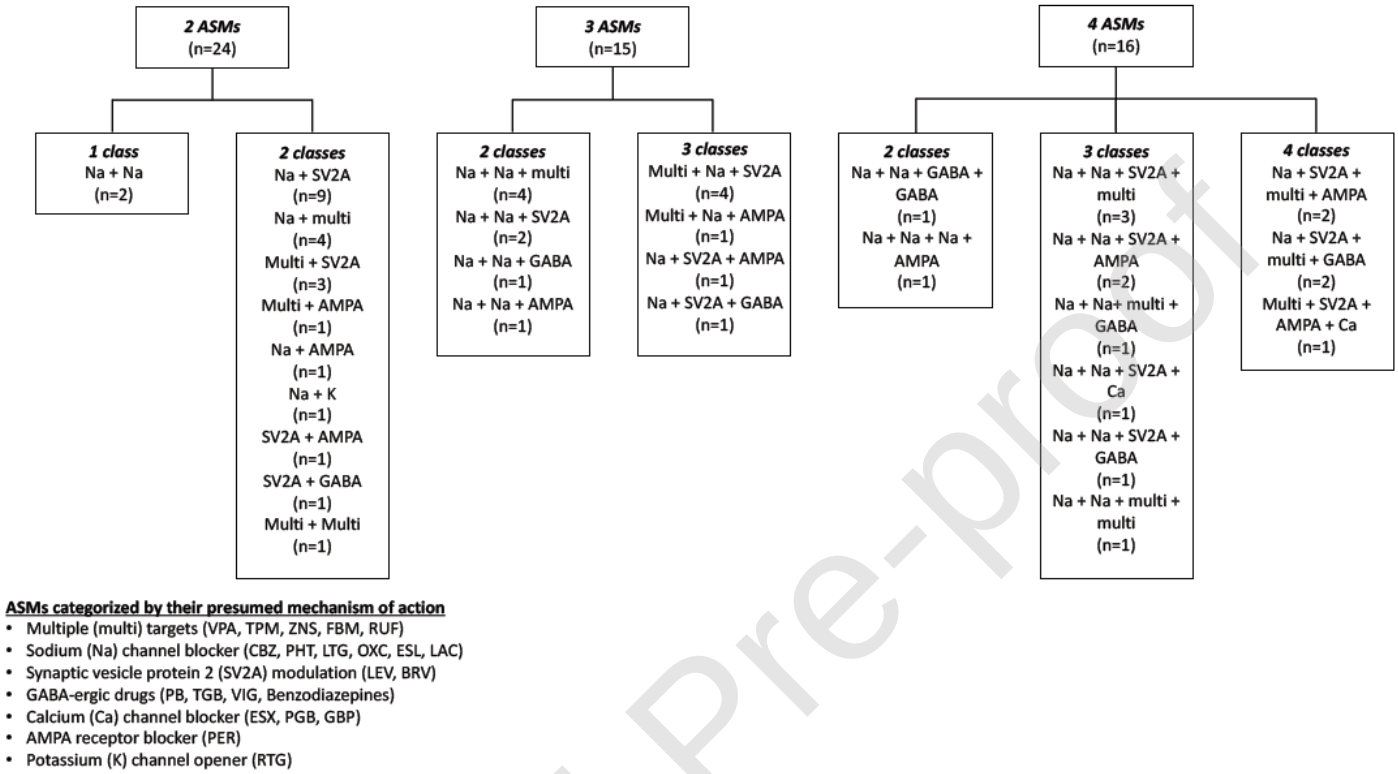

Figure 1 legend:

The ASM regimens used in those who experienced seizure freedom or greater than 75% reduction in seizure frequency, categorized by their presumed mechanisms of action are shown. Of the 11 patients who responded on monotherapy, 8 switched to an ASM with an alternative pharmacological target. 53 of the 55 combination therapy 'responders' were taking at least 2 drugs from different mechanistic groups: 40 patients on ASMs from 2 different classes; 16 patients on ASMs from 3 different classes; 5 patients on ASMs from 4 different classes.

Figure 2 title:

ASM introductions temporally related to apparent treatment response

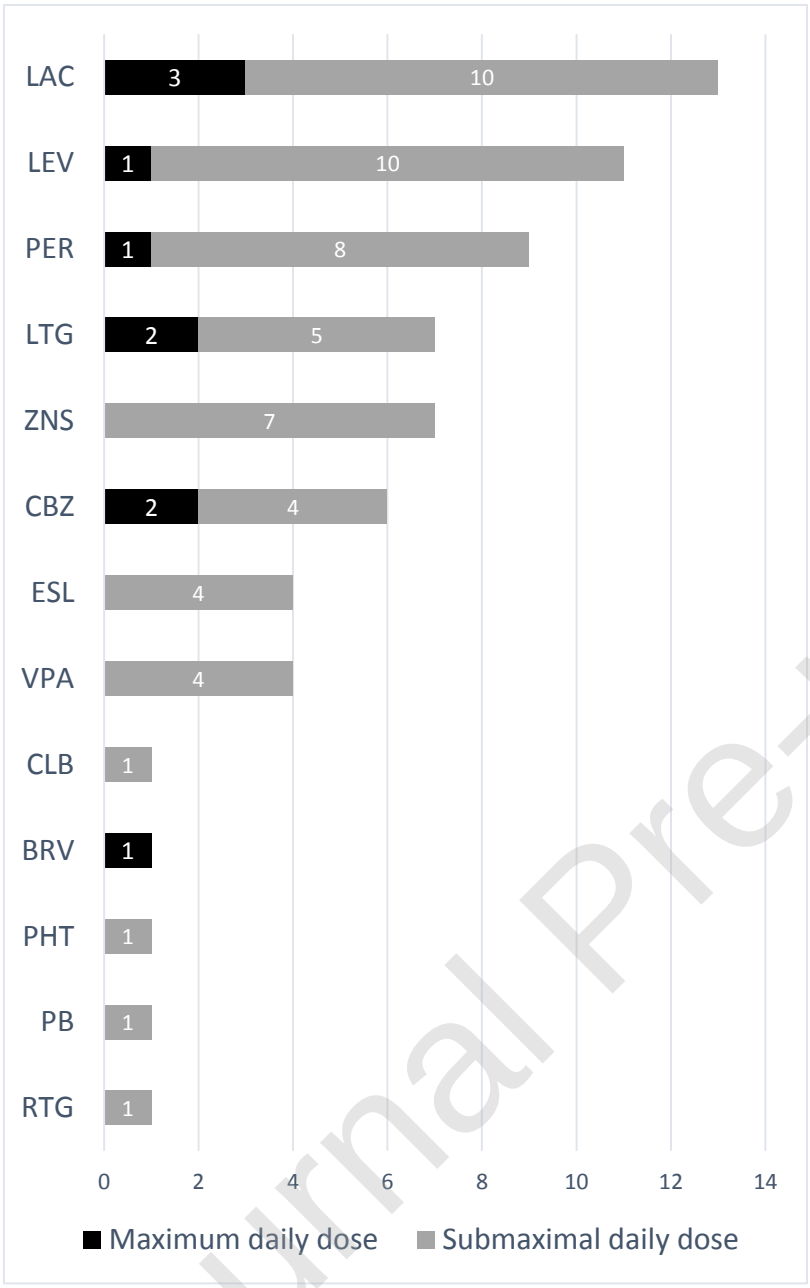

Figure 2 legend:

The ASM introductions temporally related to treatment response are shown. In 56 cases, the response was noted at submaximal daily doses (represented by orange in graph). Approximately, 66% of the ASM additions temporally related to improved seizure control were agents licensed in the past two decades (lacosamide, levetiracetam, perampanel, zonisamide, eslicarbazepine, brivarecetam).

Abbreviations used in figure 1 and figure 2:

Multi= multiple targets; Na= sodium channel blocker; SV2A= synaptic vesicle protein 2 modulation; GABA= GABAergic drugs; Ca= calcium channel blocker; AMPA= AMPA receptor blocker; K= potassium channel opener; VPA= valproic acid; TPM= topiramate; ZNS= zonisamide; FBM= Felbamate; RUF= rufinamide; CBZ= carbamazepine; PHT= Phenytoin; LTG= lamotrigine; OXC= oxcarbazepine; ESL= eslicarbazepine; LAC= lacosamide; LEV= levetiracetam; BRV= brivaracetam; PB= phenobarbital; TGB= tiagabine; VIG= vigabatrin; CLB= clobazam; ESX= ethosuximide; PGB= pregabalin; GBP= gabapentin; PER= perampanel; RTG= retigabine; AZA= acetazolamide.