Epilepsy & Behavior 96 (2019) 175–182

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

The effect of antiepileptic drugs on epileptiform discharges in genetic generalized epilepsy: A systematic review

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ARTICLE INFO

Article history:
Received 22 December 2018
Revised 2 February 2019
Accepted 14 April 2019
Available online 28 May 2019

Keywords:
Antiepileptic drugs
EEG
Generalized epilepsy
Treatment response
Seizure control
Cognition

ABSTRACT

Objective: The objective of this study was to evaluate the current evidence regarding the effect of antiepileptic drugs (AEDs) on epileptiform discharge (ED) burden in genetic generalized epilepsy (GGE).
Methods: We conducted a comprehensive literature search of PubMed, Embase, PsycINFO, and the Web of Science Core Collection databases using the keywords 'genetic generalized epilepsy', 'antiepileptic drugs' and 'epileptiform discharge'. Primary human studies published in English that reported the effect of AEDs on EDs captured on electroencephalogram (EEG) recordings of at least 24 h in duration in patients with GGE were included.
Results: Six studies published between 1984 and 2017, which reported the effect of AEDs on EDs, involving a total of 116 patients with GGE, were analyzed. Our systematic review found a tendency for AEDs to reduce ED density, frequency, cumulative duration, and burst duration in GGE. Furthermore, we found evidence that the AED-mediated reduction in ED burden was associated with improved seizure control and cognitive outcomes.
Conclusions: Antiepileptic drugs tend to reduce ED burden in GGE, but the significance of this association remains uncertain.

1. Introduction

Conventionally, patient- or third party-reported seizure frequency is used to measure response to antiepileptic drugs (AEDs) [1]. However, patients are often unaware of seizures and epileptiform discharges (EDs) when they occur [2,3]. Therefore, ED burden in the electroencephalogram (EEG) rather than reported seizure frequency may be a more reliable measure of disease burden [4–9]. Additionally, ED burden may be a better estimate of prognosis including cognitive deficits [7,10–12]. For those reasons, long-term EEG recordings measuring ED burden may potentially offer a more objective biomarker of prognosis and clinical response after AED initiation [13,14]. However, little is known about the quantitative effect of AEDs on EDs in both focal and generalized epilepsies. Because of pathophysiologic differences in the generation of EDs, the value of it as a biomarker in focal and generalized epilepsies has to be studied separately.

We pooled the studies based on EEGs recorded for at least 24 h to report the effect of AEDs on EDs in genetic generalized epilepsy (GGE) in order to answer the question 'Do AEDs reduce the ED burden in GGE?'. Current evidence regarding AED-mediated changes in ED density, frequency, cumulative duration, and ED burst duration in GGE was evaluated. We aimed to identify gaps and limitations in the current literature that can guide future research regarding AED-mediated changes in EDs in GGE. Our review also addresses the use of EEG features as biomarkers of seizure control and prognosis including cognitive outcomes. Finally, it focuses on the use of 24-hour ambulatory EEGs in the measurement of treatment response. We hope that results of this systematic review will help design future research in this field.

2. Methods

We conducted a comprehensive literature search of PubMed, Embase, PsycINFO, and the Web of Science Core Collection databases from their inception to February 2018 using the search strategy described in Table 1. In brief, key search words included variations and synonyms of the terms 'idiopathic generalised epilepsy', 'antiepileptic drugs', and 'epileptiform discharges'. Boolean operators were used to combine the search terms. We formulated this systematic review based on the Preferred Items Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15,16].

Primary human studies published in English that reported the effect of AEDs on EDs, captured on EEG recordings of at least 24 h in duration in patients with GGE, were included. The EEG recordings of at least 24 h were chosen to account for the circadian variations in EDs in GGE [17–

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https://doi.org/10.1016/j.yebeh.2019.04.030
1525-5050/

Table 1
The search strategy used in a comprehensive literature search.

1	"idiopathic generalized epilep*" OR "idiopathic generalized epilep*" OR "primary generalized epilep*" OR "primary generalized epilep*" OR "genetic generalized epilep*" OR "genetic generalized epilep*"
2	AED* OR antiepileptic* OR anti-epileptic* OR "antiepileptic drug*" OR "anti-epileptic drug*" OR "anti-epileptic medication*" or "antiepileptic medication*"
3	"epileptiform discharge*" OR "epileptiform activit*" OR epileptiform* OR discharge* OR "seizure activit*" OR "spike–wave discharge*" OR "spike–wave activit*" OR "spike–wave*" OR "spike-and-wave*" OR "polyspike" OR "poly-spike" OR "polyspike–wave*" OR "polyspike wave*" OR "poly-spike–wave*" OR "poly-spike wave*" OR "photoparoxysmal response*" OR EEG* OR electroencephalography* OR electroencephalogram*
4	1 AND 2 AND 3
5	Limit 4 to the English language

19]. Other exclusion criteria were as follows: non-English papers, nonprimary studies, animal studies, and gray literature.

The title and abstracts of English records identified through database searching were screened by one reviewer (CG) to identify relevant articles. The full-texts of articles that passed title and abstract screening were then assessed by one reviewer (CG) according to the eligibility criteria. When there was uncertainty regarding a paper's eligibility, the full-text was assessed by two additional reviewers. The reference lists of all included papers were then reviewed to identify relevant papers not detected in the initial search. The Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines and strengthening the reporting of observational studies (STROBE) guidelines were subsequently applied to ensure the quality of individual studies included in this review [20–23].

We created a data extraction sheet based on Cochrane public health data extraction template [24]. Our data collection sheet included a detailed breakdown of study characteristics under four subheadings: study design, sample size, intervention, and outcomes (Table 2).

3. Results

3.1. Study selection

Our final analysis included six studies involving a total of 116 patients with GGE (range n = 1–59) from four countries published between 1984 and 2017 reporting the effect of AEDs on EDs (Fig. 1). The gender distribution consisted of 47 males and 69 females.

Table 2
Key components of the data collection sheet.

	Subheading
1	Prospective or retrospective study design
2	Sample size • Intervention vs control group • Subsyndromes of GGE: Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME), IGE with Generalized Tonic–Clonic Seizures only (IGE-GTCSO) and Eyelid Myoclonia with Absences (EMA) • Treatment-naïve • Sample size calculations
3	Intervention • AED intervention drug • AED intervention mean dosage • Mean follow up duration after intervention commencement
4	Outcomes • AED-mediated changes in ED density • AED-mediated changes in ED frequency • AED-mediated changes in ED duration • Seizure control • Cognitive outcome

3.2. Study design

Five out of six studies were prospective (Supplementary Table). While a randomized controlled trial (RCT) on levetiracetam therapy in newly diagnosed absence epilepsy was the only study with a separate control group, other studies adopted a crossover trial design where patients in the intervention group served as their own controls as baseline 24-hour EEG were recorded before and after AED therapy [25]. Additionally, the RCT was the only study that calculated the required sample size [25]. All six studies include 24-hour EEG recordings, with synchronous video acquisition in two (Table 3).

3.3. Cohort characteristics

Across the six studies, eight patients with juvenile myoclonic epilepsy (JME), 48 with childhood absence epilepsy (CAE), 10 with juvenile absence epilepsy (JAE), and two with eyelid myoclonia with absences (EMA) who received the AED interventions were evaluated. The subtype of GGE was not specified in the remaining 27 patients. None of the six studies comprised of a homogeneous sample of a single GGE syndrome. However, two studies evaluated a cohort of absence epilepsies (CAE and JAE) [25,26]. In both cohorts, CAE formed the majority. Three studies do not specify the syndrome of GGE among their study participants [4,8,28]. Half of the studies evaluated a cohort of patients with treatment-naïve GGE [25,26,28]. Two studies assessed patients with treatment-resistant GGE [4,8], whereas one study evaluated cohorts of patients with both treatment-naïve and treatment-resistant GGE [27].

3.4. AED intervention

The six studies are heterogeneous with regard to the AED intervention used. Only the treatment effect of four AEDs was studied across the six studies: one marijuana (MAR), three levetiracetam (LEV), one sodium valproate (VPA), and one combination of drugs with all arms including ethosuximide (ETM). Moreover, only four studies reported the mean dosage of the AED intervention studied [8,25,27,28].

3.5. Follow-up

With the exception of the RCT by Fattore et al., which had a 24-hour EEG follow-up time of 0.5 months, the other five studies had follow-up times of 4 to 10 months after commencement of the AED intervention [25].

3.6. Summary of results across studies

3.6.1. Effect of AEDs on ED density in GGE

Only two studies evaluated the effect of AEDs on ED density [4,8]. Moreover, these two studies evaluated different AEDs. Sivakumar et al. studied MAR, and Rocamora et al. evaluated LEV [4,8]. Furthermore, only a total of nine GGE patients with treatment-resistant GGE were studied between these two studies (Table 4).

The two studies measured ED density differently. While Sivakumar et al. measured density as ED events per hour, Rocamora et al. calculated density as spikes per hour where all spikes are considered as individual spikes even if they were part of ED complexes, e.g., Spike–wave complexes [4,8]. This difference in the assessment of ED density makes comparisons between the findings difficult.

3.6.2. Effect of AEDs on ED frequency in GGE

Epileptiform discharge frequency was measured as the number of ED events on EEG recording. While three studies reported the percentage change in ED frequency, one study reported the number of subjects who experienced changes in ED frequency [25–28]. Four studies reported the effect of AEDs on ED frequency in a total of 86 patients

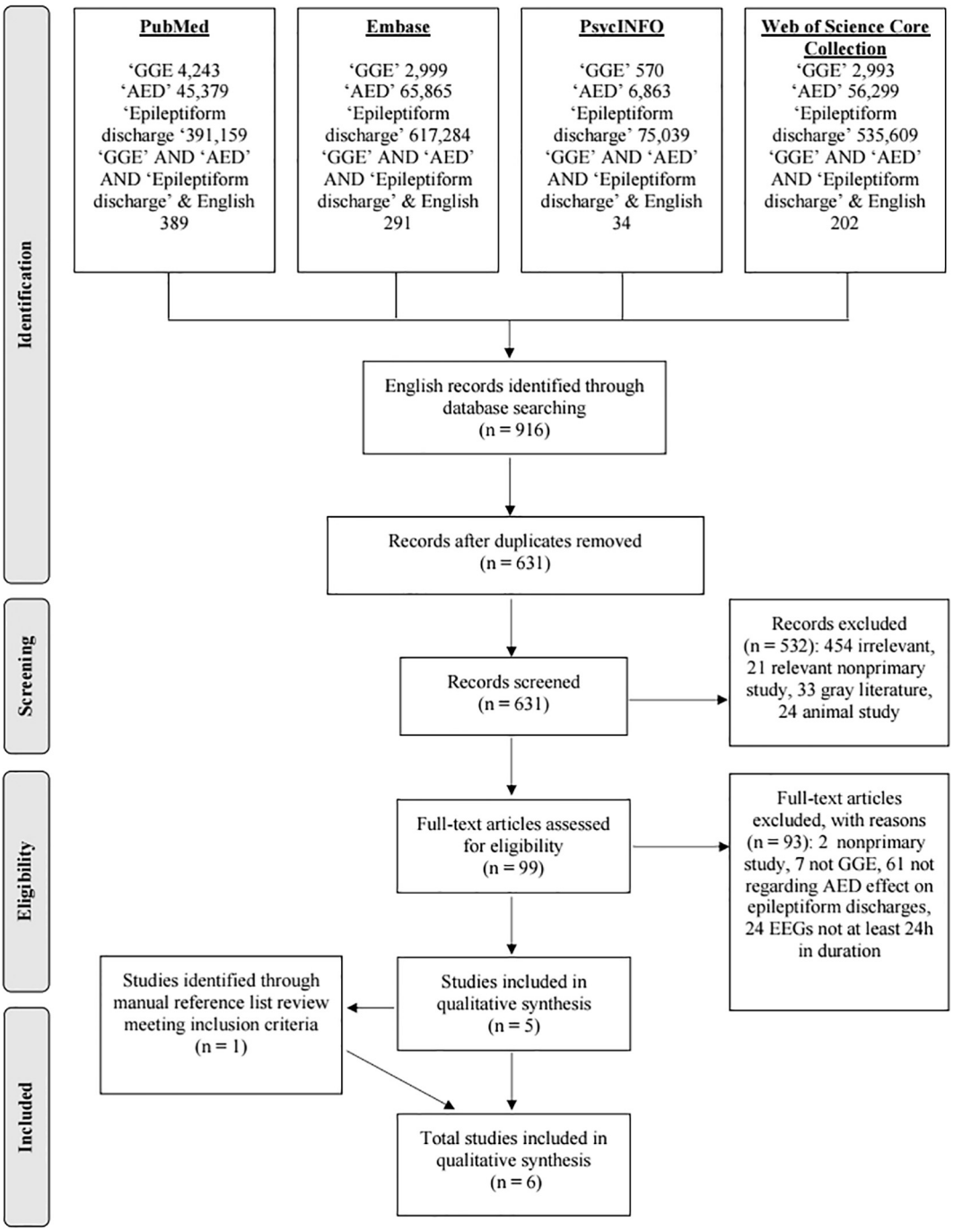

Fig. 1. Summary of the literature search strategy.

with GGE (Table 5) [25–28]. However, only the RCT commented on the statistical significance of their findings [25].

3.6.3. Effect of AEDs on ED duration in GGE

Two studies measured cumulative ED duration as the total duration of ED over the whole EEG recording, whereas others measured ED burst duration as the time from the onset to the offset of a burst of EDs [8,25,28].

Three studies reported on the AED-mediated change in cumulative ED duration (Table 6) and ED burst duration (Table 7) in a total of 64 patients with GGE with nearly two-thirds having CAE, 26 unspecified GGE subtypes and a minority JAE [8,25,28].

3.6.4. Association between changes in ED parameters and seizure control

Five studies reported the observed or patient-reported seizure control of study participants after the commencement of AED intervention [8,25–28]. In all studies, improvement in seizure control corresponded to an observed decrease in ED parameters though statistical significance is uncertain (Table 8).

3.6.5. Association between changes in ED parameters and cognitive outcomes

Only one study reported the change in cognitive outcomes after AED commencement (Table 9) [26]. They evaluated the change in fine-motor performance, attention, visual memory, spatial memory, verbal

Table 3
Summary of EEG techniques used among included studies.

Study	EEG technique — baseline assessment	EEG technique — after intervention commencement
Sivakumar, S. et al. (2017). [4]	24-hour vEEG	*C. indica*: 72-hour aEEG *C. indica/sativa*: 48-hour aEEG
Fattore, C. et al. (2011). [25]	Standard EEG (with hyperventilation and IPS) + 24-hour aEEG	Day 7: standard EEG (with hyperventilation and IPS) + 3-hour EEG with nap Day 14: Standard EEG (with hyperventilation and IPS) + 24-hour aEEG
Siren, A. et al. (2007). [26]	24-hour vEEG	24-hour vEEG
Rocamora, R. et al. (2006). [8]	24-hour EEG	24-hour EEG
Di Bonaventura, C. et al. (2005). [27]	standard EEG with photic stimulation +24-hour aEEG	2nd month: standard EEG 4th month: standard EEG 6th month: 24-hour aEEG
Stefan, H. et al. (1984). [28]	24- to 48-hour aEEG	24- to 48-hour aEEG

vEEG = EEG with video-accompaniment. aEEG = ambulatory EEG. NS = not specified. LEV = levetiracetam. VPA = sodium valproate. ETM = ethosuximide.

intelligence quotient (IQ), and performance IQ 10 months after the introduction of VPA and/or ETM in 11 patients with absence epilepsy compared with 10 age- and gender-matched controls [26]. The study group showed significant improvements in fine-motor fluency in both dominant ($p = 0.047$) and nondominant ($p = 0.022$) hands, attention ($p = 0.036$), and visual memory ($p = 0.008$). In contrast, the control group did not show significant improvements in nondominant hand fine-motor fluency ($p = 0.594$), and visual memory ($p = 0.813$). Therefore, it can be inferred that the commencement of VPA and/or ETM improved nondominant hand fine-motor fluency and visual memory in patients with absence epilepsy. This study found that this AED-mediated improvement in nondominant hand fine-motor fluency and visual memory was associated with a reduction in ED frequency in 10 out of 11 patients [26].

4. Discussion

4.1. Summary of key findings

Our systematic review found a tendency for some AEDs to reduce the burden of EDs in GGE. Furthermore, we found evidence that the AED-mediated reduction in ED burden was associated with improved seizure control and cognitive outcomes. However, there is only limited data available on the statistical significance of these associations.

In the reviewed literature, the burden of epileptiform discharges in GGE has been measured in terms of ED density, frequency, cumulative duration, and burst duration. There is preliminary evidence suggesting that MAR significantly reduces ED density [4]. While LEV, VPA, and ETM cause a reduction in ED frequency, the statistical significance of this effect is not well-elucidated [25–28]. Additionally, LEV and VPA reduce cumulative ED duration and ED bust duration [8,25,28].

A few studies have evaluated the prognostic relevance of ED burden. Five studies found that reduced ED burden corresponded with improved seizure control, whereas one study reported that decreasing in ED frequency was associated with improvements in nondominant hand fine-motor fluency and visual memory in children with CAE and JAE [8,25–28].

4.2. Statistically significant findings

In our review, only two studies reported statistically significant changes in ED burden with AED therapy. Sivakumar et al. found that MAR use was associated with a statistically significant reduction in density (events/hour) of ED events lasting <10 s ($p < 0.0004$) and ≥10 s ($p = 0.002$) in duration [4]. Rocamora et al. found that LEV use was associated with a significant reduction in both median ($p < 0.05$) and maximum ($p < 0.05$) spike–wave burst duration [8]. However, a cautious interpretation of these results is warranted due to certain study limitations.

The study by Sivakumar et al. was only a single case report [4]. The background AEDs varied during the three long-term EEG recordings and each of the long-term EEG recordings was of a different duration: 24, 72, and 48 h respectively. While the route of administration was inhalation, the type of marijuana varied, with the use of *Cannabis indica* initially, and *C. indica* and *C. sativa* later. These variables may have confounded the EEG outcome.

Similarly, there are some limitations in the study by Rocamora et al. warranting cautious interpretation of their results [8]. A study with only eight subjects might be too small to draw robust conclusions regarding the effect of LEV on ED burden in GGE. While the timing of the second 24-hour EEG was decided on clinical grounds, the study does not specify what criteria or variables were factored into this decision [8]. Variable changes were made to baseline AEDs during the LEV intervention phase of the study. As most patients had their baseline number of AEDs and/or dose of AEDs reduced during LEV treatment, the effect of LEV on EDs in GGE could have been underestimated.

4.3. Common trends without statistical significance or inferences

In our review, four out of six studies reported a reduction in ED frequency after AED commencement [25–28]. In the RCT the reduction in

Table 4
Summary of antiepileptic drug effect on epileptiform discharge density.

Study	Measure	Intervention	Baseline	After intervention	p-Value	Statistical technique
Sivakumar et al. [4]	Generalized SWD and/or diffuse paroxysmal fast wave activity <10 s events/hour	*Cannabis indica*	14	4.5	0.001	Variance analysis
		Cannabis indica/sativa		12.7	0.629	
		MAR		NS (inverse correlation)	<0.0004	Time series analysis using a GARCH
	Generalized SWD and/or diffuse paroxysmal fast wave activity ≥10 s events/hour		NS	NS (positive correlation)	0.087	Variance analysis
				NS (inverse correlation)	0.002	Time series analysis using a GARCH
Rocamora et al. [8]	Median spikes/hour	LEV	24.5	3.1	0.123	Wilcoxon signed rank test

SWD = spike–wave discharge. MAR = marijuana. LEV = levetiracetam. NS = not specified. GARCH = Generalized Autoregressive Conditional Heteroscedasticity.

Table 5
Summary of antiepileptic drug effect on epileptiform discharge frequency.

Study	Measure	Intervention	Baseline	After intervention	After placebo	p-Value	Statistical technique
Fattore et al. [25]	Percentage change in frequency of SWD bursts ≥4 s	LEV	NA	−10 ± 80%	−7 ± 33%	0.856	two-tailed Fisher's exact test
Siren et al. [26]	Number of subjects with abolished generalized SWDs	ETM (n = 5) VPA (n = 4)		7/11	NA	NS	NS
	Number of subjects with reduced frequency of generalized SWDs	ETM + VPA (n = 2)		3/11			
	Data not reported			1/11		NA	NA
Di Bonaventura et al. [27]	Average percentage reduction in the frequency of ED	LEV		60%		NS	NS
Stefan et al. [28]	Mean percentage reduction of the frequency of S-W paroxysms ≥1 s	VPA		>90%			

SWD = spike–wave discharges. ED = epileptiform discharges. S-W = spike–wave. LEV = levetiracetam. ETM = ethosuximide. VPA = sodium valproate. NA = not applicable. NS = not specified.

ED frequency did not reach statistical significance [25], whereas the significance was not reported in other three [26–28]. These studies provide preliminary evidence suggesting that VPA, ETM, and LEV may reduce ED burden in treatment-naïve and treatment-resistant GGE.

Two studies used arbitrary duration cutoffs when evaluating ED frequency. Fattore et al. only analyzed ED events of at least 4 s [25], while Stefan et al. only evaluated ED bursts of at least 1 s [28]. Therefore, the results of these studies are not directly comparable.

The study of Siren et al. involved adding on VPA in four patients, ETM in five patients, and both VPA and ETM in 2 patients [26]. However, they analyzed the effect of VPA and/or ETM on ED frequency across the cohort as a whole. This could confound the result of the study as VPA and ETM might have different effects on ED frequency. Furthermore, there appears to be a selection bias in this study as they excluded the data on the remaining patient who continued to have clinical absence seizures [26].

Di Bonaventura et al. evaluated patients with different subtypes of GGE [27]. Four patients with CAE, five with JAE, eight with JME, and two with EMA were evaluated with a mix of patients that had treatment-naïve (n = 6) and treatment-resistant (n = 13) epilepsies. Levetiracetam is known to be efficacious for generalized tonic–clonic and myoclonic seizures, but its effect specifically on absence seizures remains unknown [29,30]. If varying treatment effects across seizures types occur, a differential treatment response may account for any changes observed.

4.4. The relationship between epileptiform discharge burden and prognostic outcomes

Five out of six studies included in the final analysis reported on the seizure control of study participants with the AED intervention (Supplementary Table). In those five studies, changes in seizure control corresponded to observed changes in ED parameters. The RCT reported that the reduction in ED number, cumulative duration, and seizure control did not reach statistical significance 14 days after LEV commencement. In the other four studies, improvement in ED parameters after AED commencement was associated with improvement in seizure control. However, the statistical significance of this association was not reported.

The findings of Siren et al. suggest that there may be a significant association between reduction of ED frequency and improvement in non-dominant hand fine-motor fluency and visual memory in patients with absence epilepsy [26]. However, as previously discussed, methodological limitations preclude robust conclusions regarding the association between ED burden and cognitive outcomes.

4.5. Measurement of AED-treatment response and potential biomarkers in GGE

Conventionally, seizure frequency reported by the patient or a third party is used to measure the response to AEDs [1]. However, patients are often unaware of seizures when they occur. Patients may be unaware of up to 60% of their seizures when they are awake, and up to 80% of their seizures during sleep [2,3]. Furthermore, patients may not be aware of epileptiform discharges when they occur [12,14]. For these reasons, patient-reported or third party-observed seizure frequency may not be a reliable measure of AED-treatment response.

Long-term EEG recordings measuring ED burden may potentially offer a more objective biomarker of clinical response after AED initiation [13,14]. There is evidence that EDs and high frequency oscillations (HFOs) are useful biomarkers of epileptogenesis and seizure control, while EDs may be a biomarker of cognitive outcome in epilepsy [31].

While the literature suggests that interictal spikes and HFOs are useful biomarkers of epileptogenesis, their precise relationship remains unclear. Interictal spikes are highly specific for epilepsy as they are created by paroxysmal discharges of large collections of neurons [32,33]. However, the relationship between spikes and seizure generation is controversial due to conflicting evidence [34–36]. While older studies evaluating short-term EEG found a weak association between seizure control and EDs, more recent studies assessing long-term EEG found that reduced ED burden correlates with improved seizure control [5–7,9]. The discrepancies in the results of these studies may be due to the difference in the length of EEG recordings used. As we discuss later, long-term EEG may measure ED burden more accurately because

Table 6
Summary of findings of AED effect on cumulative ED duration in GGE.

Study	Measure	Intervention	Baseline	After intervention	After placebo	p-Value	Statistical technique
Fattore et al. [25]	Number of patients with at least 50% reduction in the cumulative duration of SWD bursts ≥4 s	LEV	NA	12/38 (31.6%)	3/21 (14.3%)	0.214	two-tailed Fisher's exact test
	Percentage change in the cumulative duration of individual EDs			3 ± 98%	−9 ± 31%	0.592	
Stefan, H. et al. (1984) [28]	Mean percentage reduction of the cumulative duration of ED bursts ≥1 s	VPA		>90%	NA	NS	NS

SWD = spike–wave discharge. ED = epileptiform discharge. LEV = levetiracetam. VPA = sodium valproate. NA = not applicable. NS = not specified.

Table 7
Summary of antiepileptic drug effect on epileptiform discharge burst duration.

Study	Measure	Intervention	Baseline	After intervention	After placebo	p-Value	Statistical technique
Rocamora et al. [8]	Median spike–wave burst duration (seconds)	LEV	1	0.2	NA	<0.05	Wilcoxon signed rank test
	Maximum spike–wave burst duration (seconds)		6	1.5			
Stefan et al. [28]	Number of patients with reduced mean duration of ED bursts ≥1 s	VPA	NA	10/18		NS	NS
	Number of patients with increased or unchanged mean duration of ED bursts ≥1 s			8/18			

ED = epileptiform discharge. LEV = levetiracetam. VPA = sodium valproate. NA = not applicable. NS = not specified.

of its ability to account for ultradian and circadian fluctuations [17,37]. A recent study found that shorter mean duration of generalized paroxysms, lower ED counts, and lower spike density recorded on EEG are associated with longer durations of seizure freedom in GGE when analyzed retrospectively [9]. In our review, we also found that AED-mediated improvement in ED density, frequency, cumulative ED duration, and ED burst duration was associated with improved seizure control in GGE [8,26–28]. This provides further evidence to support the hypothesis that improvement in abnormal epileptiform activity may be a useful biomarker predictive of seizure control.

Recent studies also suggest that HFOs are a biomarker of epileptogenic brain tissue and the resection of regions generating HFOs predicts good surgical outcomes in refractory focal epilepsy [38]. Interictal HFOs increase with the reduction of AEDs accompanied by increased seizure occurrence [39]. Based on those observations, there is an emerging viewpoint that HFOs are useful biomarkers of disease activity in epilepsy [40]. Studies on HFO in GGE are scarce. One study reported higher HFO rates accompanied by ictal ED compared to interictal ED in CAE [41].

Transient cognitive impairment (TCI) is commonly associated with generalized EDs in epilepsy [10]. One study proposed that improved alertness and behavior after AED changes are due to reduced interictal EDs [7]. Furthermore, up to 50% of patients with EDs during cognitive assessment are found to have TCI [11]. This suggests that EDs may impact cognitive ability in epilepsy or are a marker of more severe disease associated with cognitive impairment. A more recent study has found that in GGE, poorer memory and cognitive function was associated with a greater cumulative duration of EDs recorded on 24-hour EEGs [12]. Moreover, the same study found that variation in the estimate of IQ is explained more by the total ED duration during sleep compared with that during wakefulness [12]. Furthermore, the changes in long-term memory function were explained more by the total ED duration during wakefulness compared with that during sleep [12]. Antiepileptic drug-mediated reduction in ED number was associated with significant improvement in nondominant hand fine-motor fluency and visual memory [26]. This result provides additional evidence supporting the use of ED burden as a biomarker of cognitive outcome in epilepsy.

4.6. Preferred EEG technique in the measurement of AED-treatment response

Epileptiform discharges may be considered a useful biomarker of AED-treatment response as there is evidence that they are correlated with seizure control and cognitive outcomes in epilepsy [26]. Twenty-four hour ambulatory EEG (aEEG) appears to be better than shorter EEG methods of capturing the burden of interictal abnormal EDs because of temporal variation in discharges in GGE suggesting the timing of EEG is critical in estimating treatment changes [17].

Epileptiform discharges have an intimate relationship with the sleep–wake cycle in GGE [42]. One-third of EDs occur in wakefulness and two-thirds occur in nonrapid eye movement (NREM) sleep [17]. Therefore, recording an EEG during natural sleep increases the diagnostic yield. This finding underscores the practical importance of recording the EEG for at least 24 h, preferably in the subject's own environment to encourage natural sleep [17].

Over several decades, studies have described the temporal patterns of seizures [43–47]. However, there are emerging studies that evaluate the temporal patterns of EDs [17–19,48–51]. A recent study found ultradian (<24 h) and infradian (weeks to months) fluctuations in EDs adding to the complexity of timing and duration of comparative EEG estimates when measuring the change in the burden of ED [37]. Studies have also found a circadian pattern in the occurrence of EDs [17–19,48,49]. A more recent study found that EDs follow a circadian pattern regardless of the duration of EDs, i.e., ED fragments versus more prolonged generalized ED [17]. This study found that EDs peak between 11 pm–7 am, and 12 noon–4 pm [17]. The distribution of EDs was found

Table 8
Summary of findings of AED effect on seizure control. (LEV = levetiracetam. ETM = ethosuximide. VPA = sodium valproate. NA = not applicable. NS = not specified).

Study	Measure	Intervention	Baseline	After intervention	After placebo	p-Value	Statistical technique	Reported changes in ED parameters
Fattore et al. [25]	Number of patients free from clinical seizures on days 13 and 14, and EEG seizures on day 14 (standard EEG)	LEV	NA	9/38 (23.7%)	1/21 (4.8%)	0.08	two-tailed Fisher's exact test	Reduction in ED frequency and cumulative duration not statistically significant.
Siren et al. [26]	Number of children with absence seizures during 24-hour video-EEG recording	ETM (n = 5) VPA (n = 4) ETM + VPA (n = 2)	11/11	1/11	NA	NS	NS	Reduced ED frequency. No comment on statistical significance.
Rocamora et al. [8]	Number of seizure-free patients	LEV	NA	5/8				Reduction in ED density not statistically significant. Significant reduction in ED burst duration.
	Number of patients with >50% reduction in seizure frequency			2/8				
	Number of patients with worsening of seizure frequency			1/8				
Di Bonaventura et al. [27]	Number of seizure-free patients			13/19				Reduced ED frequency. No comment on statistical significance.
	Number of patients with 50–75% reduction in seizure frequency			5/19				
	Number of patients with unchanged seizure frequency			1/19				
Stefan et al. [28]	Number of seizure-free patients	VPA		10/18				Reduced ED frequency and cumulative duration. No comment on statistical significance.
	Number of patients with reduced seizure frequency			6/18				
	Data not available			2/18				

Table 9
Summary of results from the Siren et al. [26] study.

p value	Study group	Control group
Verbal IQ	0.286	0.033
Performance IQ	0.123	0.091
Fine-motor fluency		
• Dominant hand	• 0.047	• 0.015
• Nondominant hand	• 0.022	• 0.594
• Dominant/nondominant hand difference	• 0.333	• 0.028
Attention	0.036	0.012
Visual memory	0.008	0.813
Spatial memory	0.074	0.063

to have toughs at 6 pm–8 pm and 9 am–11 am [17]. Twenty-four hour EEGs are likely to capture all the peaks and troughs resulting from the circadian and ultradian pattern of EDs. Capturing infradian ED fluctuations would require EEGs of weeks to months in duration and poses more logistic challenges.

Twenty-four hour ambulatory EEG may be the best compromise method for measuring EDs in GGE because of its accessibility, diagnostic yield, and ability to capture ED temporal fluctuations. Compared to inpatient video-EEG, 24-hour ambulatory EEG is 75% cheaper and better tolerated by patients [1,52].

4.7. Applications in focal epilepsy

Though not our main objective in the review, it would be pertinent to examine data from studies on focal epilepsies. The value of interictal epileptiform discharges captured on 24-hour ambulatory EEG in predicting seizure recurrence following AED withdrawal has been shown in some studies [53,54]. A systematic review found that the presence of interictal epileptiform discharges in the postoperative EEG was associated with an unfavorable outcome after epilepsy surgery (odds ratio [OR]: 3.3; 95% confidence interval [CI]: 2.5–4.5) [55]. Given the burden and potential consequences of refractory focal epilepsy, more research on the interactions among focal epilepsy, epileptiform discharges, AED, and prognostic outcomes is warranted.

4.8. Strengths

All studies included in this review utilized EEG recordings of at least 24 h in duration. All six studies recorded 24-hour EEGs before AED commencement to act as a baseline. This allowed their study participants to serve as their own controls. Five out of six studies had cohorts homogenous for either treatment-resistant or treatment-naïve GGE. The majority of the six studies reported the AED-mediated change in ED number and seizure control.

4.9. Limitations

There is only one randomized controlled trial [25]. There is a sampling bias towards CAE with only a few patients with JAE, JME, and EMA being studied. Moreover, all six cohorts are heterogeneous for GGE syndromes, and one cohort is heterogeneous in terms of treatment-resistant or treatment-naïve GGE. The sample size required to power the studies was calculated only in the RCT [25]. The six studies are also heterogeneous in terms of the AEDs evaluated with only four AEDs being studied — MAR, LEV, VPA, and ETM. The mean follow-up duration after AED commencement among studies varied. Furthermore, only one out of six studies reported AED-mediated changes in ED frequency, cumulative duration, and ED burst duration [28]. Additionally, only one study reported the cognitive outcome of their cohort after AED commencement [26]. Cognition in epilepsy is a complex subject and AED therapy is a confounding variable in studies measuring cognitive outcomes. Therefore, no firm conclusions can be drawn from this single study.

4.10. Gaps in knowledge

The effect of AEDs on estimates of ED burden in GGE remains uncertain because of the paucity of studies that report the statistical significance of this effect. Little is known about AED-mediated ED changes in GGE syndromes other than CAE as fewer patients in these populations have been evaluated. Furthermore, there remains a knowledge gap regarding the strength of association between AED-mediated ED changes and long-term prognosis including seizure control and cognitive outcomes although cognitive dysfunction in GGE is an increasingly recognized comorbidity [12]. It is unclear what the best measurement is in quantifying epileptiform discharges and the methodologies vary among studies. We hope that results from our analysis will serve as a foundation for future research in this space.

4.11. Future research directions

Prospective studies with a larger sample size evaluating the effect of AEDs on EDs in GGE would be valuable in quantifying the association between AED therapy and ED burden. Studies utilizing more prolonged EEG recordings are needed to account for the circadian and infradian changes in EDs. Those studies should also shed light on the best parameter of ED burden, as current studies have used variable measures ranging from the ED density to ED burst duration. Moreover, cohorts homogenous with respect to the subtype of GGE, and treatment response status (naïve vs resistant), prospectively evaluated with appropriate controls and standardized AED interventions are recommended to avoid further confounding of results. Future studies with cohorts of JAE, JME, idiopathic generalized epilepsy with generalized tonic–clonic seizures only (IGE-GTCSO), and EMA would fill the gap in the current literature regarding the effect of AEDs on EDs in these patient populations. Furthermore, there is a need for studies comparing the impact of all broad-spectrum AEDs on ED in GGE as no clear conclusions can be drawn from the current literature regarding the class effect of different AEDs. These studies should also evaluate the effect of treatment on the long-term prognosis as well as important co-morbidities associated with GGE particularly cognition, mood, sleep, anxiety, and the effect on educational and occupational trajectories. Quantifying ED manually is a labor-intensive and time-consuming process limiting its practical applications. Hence, research into automated ED detection and quantification is needed to incorporate this into routine clinical practice. Finally, there is a growing need to evaluate more biomarkers such as HFOs in GGE to understand the complex interplay among biomarkers, AEDs, and prognostic outcomes including seizure control and cognition.

5. Conclusions

Our systematic review reveals a trend toward improved seizure-related outcomes with reduced ED burden as a result of AED therapy in GGE. Given the many limitations in the published literature on this subject, further research is needed to unravel the complex relationship among ED burden, AED therapy, and prognostic outcomes.

Disclosure of conflict of interest

Wendyl D'Souza's salary is part-funded by The University of Melbourne. He has received travel, investigator-initiated, and speaker honoraria from UCB Pharma; investigator-initiated and speaker honoraria from Eisai Australia educational grants from Novartis Pharmaceuticals, Pfizer Pharmaceuticals, and Sanofi-Synthelabo; educational, travel, and fellowship grants from GSK Neurology Australia, and honoraria from SciGen Pharmaceuticals. The remaining authors have no conflicts of interest.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.04.030.

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