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Newer antiepileptic drugs in status epilepticus: prescription trends and outcomes in comparison with traditional agents

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Running head : Evaluating newer antiepileptic drugs in status epilepticus

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Abstract

Introduction

Newer antiepileptic drugs (AEDs) are increasingly prescribed; however, relatively limited data are available concerning their use in status epilepticus (SE) and the impact on outcome.

Objectives

To explore the evolution in prescription patterns of newer and traditional AEDs in this clinical setting, and their association with prognosis.

Methods

We analyzed our prospective adult SE registry over 10 years (2007-2016), and assessed the yearly use of newer and traditional AEDs and its association with mortality, return to baseline condition at discharge, and SE refractoriness defined as treatment resistance to 2 AEDs including benzodiazepines.

Results

In 884 SE episodes, corresponding to 719 patients, prescription of at least a newer AEDs increased from 0.38 per SE episode in 2007 to 1.24 per SE episode in 2016 (mostly due to levetiracetam and lacosamide). Traditional AEDs (excluding benzodiazepines) declined over time from 0.74 in 2007 to 0.41 in 2016, correlating with the decreasing use of phenytoin. Prescription of newer AEDs was independently associated to a lower chance of return to baseline conditions at discharge (OR 0.58, 95% CI 0.40-0.84), and a higher rate of SE refractoriness (OR 19.84, 95% CI 12.76-30.84), but not with changes in mortality (OR 1.08, 95% CI: 0.58-2.00).

Conclusion

We observed a growing trend in newer AEDs prescription in SE over the last decade. However, our findings might suggest an associated increased risk of SE refractoriness and new disability at hospital discharge. Pending prospective, comparative studies, this may justify some caution in the routine use of newer AEDs in SE.

Key findings

- Prescription of newer antiepileptic drugs (AED) in status epilepticus (SE) markedly increased during the last decade, mostly due to levetiracetam and lacosamide.

- While mortality at hospital discharge did not significantly change, use of newer AEDs was independently associated with higher SE refractoriness and disability at discharge.

- These findings are potentially concerning and, awaiting comparative studies, may justify some caution in the routine use of newer AEDs in SE.

Introduction

Status epilepticus (SE) represents one of the most frequent neurological emergencies with significant morbidity and mortality. It thus requires prompt treatment in order to avoid cerebral damage, systemic complications or death(1,2). Current SE treatment recommendations are based on a three steps approach, with benzodiazepines as first-line treatment followed by intravenous antiepileptic drugs (AEDs); if SE termination is not achieved despite the first two lines, general anesthesia and coma induction may be necessary(1–4).

AEDs are a heterogeneous group of medications with a variety of pharmacokinetic and pharmacodynamic effects. Over the past two decades, a rapid expansion in the number and type of AEDs has been witnessed, including several with intravenous formulations. AEDs are commonly divided into newer and traditional ones, according to the year of marketing (before or after 1990). In the treatment of epilepsy, newer compounds generally exhibit better tolerability and lower drug interaction with comparable efficacy to traditional AEDs(5); accordingly, a growing trend in the use of newer AEDs is being reported, although indications other than epilepsy seem to also contribute (6–10).

Several studies already analyzed the efficacy of newer AEDs in SE(11–20); however, besides a previous preliminary analysis by our group(20), little is known regarding the evolution over time in AEDs prescription patterns in SE, and its impact on clinical outcome. The aims of this study were to explore the changes in prescription of newer and traditional AEDs in SE treatment over the last decade, and their association with prognosis.

Methods

In this cohort study, we retrospectively analyzed our prospective SE registry recording data on adults with SE episodes treated in our hospital; details have been described elsewhere(21,22). Briefly, SE was defined as continuous or repetitive seizures without full recovery in between, lasting more than 30 minutes (until 2008) and more that 5 minutes (since 2008)(23). All patients were identified by the neurological consulting team and the staff of the epilepsy/EEG unit. Children under 16 years old and subjects with post-anoxic SE were not included. SE treatment

guidelines of our hospital foresee as first line a slow bolus of intravenous clonazepam 0.015mg/kg, midazolam 0.15mg/kg (which can also be given intramuscularly), or lorazepam 0.1mg/kg; and as second line, intravenous levetiracetam 30 mg/kg, valproate 30mg/kg or phenytoin 20mg/kg.

We retrieved data of SE episodes between January 1st 2007 (the first entire year after beginning of the registry) and December 31st 2016, a period encompassing the introduction in Switzerland of several newer intravenous AEDs, such as levetiracetam (2008) and lacosamide (2009). These included demographics, etiology defined as "potentially fatal" if potentially leading to death independently of SE treatment(24), the validated STESS severity score (relying on age, history of seizures, seizures type, and extent of consciousness impairment before treatment)(25), type and number of AED prescribed, coma induction for SE treatment, SE refractoriness (defined as need of more than two treatment lines) and outcome at hospital discharge. The latter was categorized as return to baseline clinical conditions, new handicap, or death(21).

AEDs were divided in two groups according to the year of marketing (before or after 1990): benzodiazepines, phenobarbital, phenytoin, valproic acid, and carbamazepine were considered "traditional AEDs". Levetiracetam, pregabalin, gabapentin, lamotrigine, lacosamide, topiramate, felbamate, retigabine, oxcarbazepine, rufinamide, perampanel and brivaracetam (used off label in our hospital at the end of 2016, as it was introduced in Switzerland in january 2017) were considered "newer AEDs". Propofol, thiopental, steroids, ketamine, etomidate, ketogenic diet, emergency surgery, or lack of treatment (spontaneous resolution of the SE episode) were considered separately.

The evolution of use of traditional (including and excluding benzodiazepines, which represent alone the first treatment line and were thus supposed to be consistently prescribed over time) and newer AEDs was reported as the yearly ratio between the total number of prescribed AEDs belonging to a given group (traditional versus newer), and the number of SE events. Of note, more than one newer or traditional AED could be used in a given episode. Frequencies of prescription of individual AEDs were then reported as percentage of the SE episodes for each year.

Statistical analysis was performed using Stata version 14 (College Station, TX, USA). To test associations with clinical outcome, univariable analyses over the whole study period were performed with Student t test and Chi2 tests as needed; stepwise multivariable logistic regressions were used to identify variables independently associated with mortality (considering patients and not episodes), return to baseline condition and refractory SE. Goodness of fit was assessed with a Hosmer-Lemeshow test.

Results

We recorded 884 SE episodes during the 10 years study period, occurring in 719 patients. Clinical characteristics are shown in **Table 1**. The yearly incidence of SE markedly increased during the studied time lapse (from 58 episodes in 2007 to 86 in 2016), while the proportions of patients with history of previous seizures or potentially fatal etiologies, as well as the proportion of SE semiological types (data not shown), remained globally stable.

Over the entire study period, traditional AEDs were prescribed 1382 times and newer AEDs 767 times. As shown in **Figure 1**, the frequency of newer AEDs use gradually increased, whereas traditional AEDs utilization remained stable over time as a whole, but decreased if excluding benzodiazepines. Globally, newer AEDs were prescribed per SE episode from 0.38 in 2007 to 1.24 in 2016; conversely, traditional AEDs without benzodiazepines decreased from 0.74 in 2007 to 0.41 in 2016.

Frequencies of use of individual AED, used in at least 10% of episodes in one year, are shown in **Figure 2**. Among traditional AEDs, phenytoin showed the most obvious decrease, while prescription of valproate and, less frequently, phenobarbital remained relatively constant. Carbamazepine was used very rarely (8 times). The prescription pattern of benzodiazepines also showed some evolution: clonazepam was most frequently and constantly administered. Lorazepam, diazepam, clobazam and oxazepam were administered uncommonly; their frequencies slightly declined. However, the use of midazolam increased as first line agent from 0% in 2007 to 15% in 2016, and as third line compound from 0% in 2007 to 9% in 2016.

Among newer AEDs, levetiracetam and lacosamide showed the major increment. In 2007 levetiracetam was used in only 30%, but from 2010, two years after introduction of its intravenous formulation in Switzerland, it was prescribed in more than 50% of SE episodes. Intravenous lacosamide was introduced together with the oral form in 2009 in Switzerland; since 2010 its utilization gradually increased: it was prescribed in nearly 40% of episodes in 2016. Even if less frequently prescribed, pregabalin also slightly increased. The use of oxcarbazepine, gabapentin, lamotrigine, topiramate, felbamate, retigabine, rufinamide, perampanel, and brivaracetam was almost negligible (respectively 3; 3; 9; 13; and 1 cases over the study period).

Among other treatments (**Figure 3**), propofol increased (6.9%, N=4/58 in 2007 vs 22.1%, N=19/86 in 2016). Further therapeutic approaches, such as thiopental, steroids, ketamine, ketogenic diet, surgery, and etomidate remained extremely rare (respectively 12; 14; 6; 3; 2; 1 cases over the study period). Finally, 1-4 patients per year did not receive any treatment, as their SE episode resolved spontaneously.

The number of refractory SE gradually increased through time **(Figure 3)** with an average of 2.17 ± 1.98 AEDs prescribed per SE in 2007 and 2.98 ± 1.5 in 2016. The mean STESS score slightly increased from 2.5 ± 1.2 in 2007 to 2.7 ± 1.5 in 2016. Need for intubation also gradually increased: in 2007 10% of patients received coma and were mechanically ventilated for SE treatment, whereas in 2016 this approach was used in 22% of SE episodes. Outcome at discharge tended to evolve towards a smaller proportion of return to baseline clinical conditions; mortality remained stable (**Figure 4**).

In univariate analyses, potentially fatal etiology, higher STESS score, intubation for SE treatment, SE refractoriness to the first two treatment lines, and newer AEDs prescription correlated with poorer prognosis, whereas higher STESS score, potentially fatal etiology, and newer AEDs were associated with refractory SE. **Table 2** illustrates the results of uni- and multivariable analyses, adjusted for recognized outcome predictors, especially SE severity (STESS) and etiology. Prescription of newer AEDs was independently correlated to a higher proportion of disability at discharge and a higher rate of treatment failures, but not with increased mortality.

These three models showed acceptable goodness of fit (P=0.33 regarding mortality, 0.19 for return to baseline condition and 0.45 regarding refractoriness).

Discussion

During the 10 years under study, the overall prescription of newer AEDs showed an important increase that was inversely correlated to that of traditional AEDs (excluding benzodiazepines). While mortality at hospital discharge did not change significantly, use of newer AEDs was independently associated with higher SE refractoriness and disability at discharge.

A similar trend of increasing prescription of newer compounds has already been described not only in SE, but more generally in patients with epilepsy and in the general population(6–10,20). In the present study, this increase was mainly due to levetiracetam and lacosamide. Only two years after the introduction of intravenous levetiracetam in Switzerland, this became the most frequently used AED in SE in our center, after benzodiazepines. This abrupt raise could be at least in part explained by the previous existence of the oral form: physicians may have been already familiar with this agent, generating a shorter adaptation time. Lacosamide became the second most frequently prescribed AED since 2015, four years after its marketing.

Regarding traditional AEDs, changes in phenytoin prescription accounted mostly for the observed reduction, whereas VPA utilization remained globally stable. The potential side effects of PHT together with the relatively difficult clinical administration (implying cardiac monitoring) and clinical follow-up (difficult pharmacokinetics and challenging pharmacokinetic interactions) could explain its decrease to the benefit of newer compounds with better tolerability, easier administration, and supposed similar efficacy (17,26).

Prescription of newer AEDs was associated with higher disability at hospital discharge after adjustment for SE severity assessed through the STESS score, SE etiology, intubation for SE treatment and, importantly, SE refractoriness. This result differs from previous assessments suggesting a comparable efficacy of newer compounds in patients with epilepsy(17,19,27–30). In those studies, the vast majority of patients had generalized convulsive SE, thus possibly limiting generalizability to

patients, like in the present cohort, including all SE types. A previous study from our group, restricted to the years 2006-2010, reported similar findings as compared to the present study(20), with a greater likelihood to receive newer AEDs in patients with more aggressive SE forms (stratified by potentially fatal etiology, higher STESS, or refractory SE). Indeed, as newer AEDs present fewer cardio-respiratory side effects, a low potential for interactions and linear pharmacokinetics properties, they could be prescribed preferentially in patients with co-medications and significant co-morbidities ("confounding by indication"). Nevertheless, our multivariable analysis was adjusted for important outcome predictors including SE and etiology severities, total number of prescribed AED, and SE refractoriness.

Finally, the number of our SE episodes almost doubled between 2007 and 2016, possibly due to the increase of EEG monitoring in the last years(31) and the detection of more aggressive SE forms in patients with altered consciousness(32). Of note, the breakdown into the different SE semiological types did not change significantly between 2007 and 2016. Nevertheless, patients treated with newer AEDs showed a higher rate of refractoriness even after correction for STESS score and etiology. This could suggest a lower efficacy of newer compounds. A potential explanation could be that newer AEDs can be administered faster than phenytoin, thus shortening the time during which the clinical response is assessed. This, in turn, might induce clinicians to consider treatment escalation quicker than previously. The increase of the proportion of patients with new handicap at discharge seems however to contradict this possibility. In line with this consideration, a recent randomized controlled trial did not disclose any benefit regarding generalized convulsive SE control after addition of levetiracetam to clonazepam(33).

Levetiracetam was by far the most frequent newer AED. Various studies, including a meta-analysis, comparing it with phenytoin or valproate, showed no difference in terms of clinical seizures cessation(17,19). However analysis from our group described a higher rate of treatment failures with levetiracetam than valproate(18). This may reflect a suboptimal SE treatment approach with insufficient doses of newer AEDs, or their prescriptions without or with underdosed benzodiazepines as first line treatment(34). However, in animal studies levetiracetam has shown a relatively slow penetration into the central nervous system, with latencies of more than 1 hour to

achieve maximum concentrations in the cerebrospinal or in the brain extra-cerebral fluid(35–37). Animal studies with phenytoin, on the other side, shows maximum concentrations in cerebrospinal and brain extra-cerebral fluids within 9-13minutes and 39-34minutes, respectively(38). This could possibly correlate with a slower clinical action of LEV and explain at least partially the relationship between refractoriness and newer AEDs.

Our study is to the best of our knowledge the fist analyzing prescription patterns of AEDs in SE over a long time period in a large and well characterized adult cohort. The SE registry being prospectively filled by the same investigators, its internal validity appears robust. We nevertheless acknowledge limitations. We assessed only prescription of AEDs, without information about treatment side effects. We aimed at describing the evolution trends of AED use in the era of newer compounds, but not at analyzing the impact of each single medication. A selection bias may be present, as we considered only patients from a university hospital; however, in our country the vast majority of SE patients are treated in larger hospitals. Due to retrospective data analysis, some confounding factors might have been at play: we used multivariable analyses to adjust for the most important known outcome predictors. However, adequacy of first line treatment, adherence to guidelines and SE duration were not assessed. Nevertheless, a previous study from our group reported no major effect of treatment adherence to guidelines on prognosis, after considerations of robust outcome predictors (etiology, STESS score) over a more restricted time lapse(39). It seems also unlikely that the poorer outcome found in patients treated with newer AEDs could be explained by a systematic difference in treatment appropriateness between the two groups. Outcome was scored at hospital discharge: an information bias may have been at play regarding newer handicap, which evolves over time. While a systematic bias seems unlikely, we underscore that mortality, being a robust variable, did not correlate with newer AEDs prescription. In any case, these considerations do not apply to SE refractoriness. SE timing definition changed in 2008; however, we extrapolate that this may have lead to miss at most only 7 episodes lasting less than 30 minutes in 2007 (corresponding to less than 1% of the total number). Finally, due to the study design, the described associations are not necessarily reflecting causality.

Conclusion

A growing trend in newer AEDs prescription in SE was observed over the last decade. However, our findings do not show a resulting prognosis improvement; rather, they seem to suggest an association with increased new disability at discharge and SE refractoriness. These findings are potentially concerning, and call for some caution in the indiscriminate use of newer AEDs in SE: the ongoing ESETT trial(40) may help elucidating this issue.

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Table 1. Clinical characteristics of the study population

Year	SE episodes (n)	Women (%)	Age (mean +/-SD)	Potentially fatal etiology (%)	History of previous seizure (%)	STESS score (mean ± SD)
2007	58	46.6	60.1± 18.1	48.3	48.3	2.5 ± 1.3
2008	79	67.1	59.5 ± 16.6	45.6	48.1	2.4 ± 1.5
2009	80	48.8	58.7 ± 19.8	37.5	60	2.3 ± 1.5
2010	93	47.3	62.9 ± 18.7	44.1	43	2.7 ± 1.3
2011	93	48.4	65.3 ± 17.0	53.8	53.8	2.7 ± 1.4
2012	93	45.2	60.8 ± 16.3	51.6	59.1	2.4 ± 1.6
2013	99	48.5	57.8 ± 20.3	41.4	50.5	2.7 ± 1.5
2014	88	45.5	58.3 ± 22.3	47.7	61.4	2.3 ± 1.6
2015	115	54.8	65.8 ± 16.2	53.1	42.6	3.2 ± 1.5
2016	86	44.2	59.9 ± 16.0	54.7	56.9	3.0 ± 1.5
2007-2016	**884**	**48.8**	**61.1 ± 18.6**	**47.9**	**52.1**	**2.6 ± 1.5**

Table 2. Variables of interest as compared to prognosis (mortality and new handicap) and Status epilepticus refractoriness (resistance to two treatment lines)

	Dead	**Alive**	*p* univariate	*p* multivariate	OR	95% CI
N (patients)	106	613				
Gender: women (%)	53.8	42.2	0.147	-		
Potentially fatal etiology (%)	76.4	46.2	<0.001	**<0.001**	3.63	2.18-6.03
STESS (mean ±SD)	3.42 ± 1.24	2.58 ± 1.5	<0.001	**<0.001**	1.38	1.17-1.61
Intubation (%)	19.8	10.4	0.006	0.605	1.18	0.63-2.23
Refractory SE (%)	67.0	40.6	<0.001	**<0.001**	3.05	1.67-5.58
AEDs/episodes (mean ±SD)	3.28 ± 1.57	2.40 ± 1.3	< 0.001	-		
Use of newer AED (%)	79.2	61.7	<0.001	0.738	0.89	0.47-1.71
	Return to baseline	**New handicap or death**	*p* univariate	*p* multivariate	OR	95% CI
N (episodes)	453	431				
Gender: women (%)	45.7	52.0	0.062	-		
Potentially fatal etiology (%)	34.4	62.2	<0.001	**<0.001**	0.35	0.25-4.79
STESS (mean ±SD)	2.20 ± 1.43	3.04 ± 1.44	<0.001	**<0.001**	0.7	0.63-0.78
Intubation (%)	6.2	17.6	<0.001	0.287	0.71	0.37-1.34
Refractory SE (%)	28.9	57.3	<0.001	0.562	0.85	0.50-1.45
AEDs/episodes (mean ±SD)	2.13 ± 1.2	3.00 ± 1.6	<0.001	**0.014**	0.75	0.59-0.94
Use of newer AED (%)	49.2	76.8	<0.001	**0.006**	0.58	0.39-0.86
	Refractory	**Non refractory**	*p* univariate	*p* multivariate	OR	95% CI
N (episodes)	378	506				
Gender: women (%)	47.1	50.0	0.39	-		
Potentially fatal etiology (%)	53.7	43.7	0.003	0.611	0.91	0.65-1.23
STESS (mean ±SD)	2.86 ± 1.55	2.42 ± 1.4	<0.001	**0.008**	1.17	1.04-1.31
Use of newer AED (%)	93.1	39.9	<0.001	**<0.001**	20.42	12.79-32.60

Figure legends

Figure 1:

Evolution of the prescription pattern of newer AEDs, traditional AEDs and traditional AEDs with exclusion of benzodiazepines. Results are expressed the yearly ratio between the total number of AEDs prescribed in a given group and the number of SE events.

AEDs : antiepileptic drugs. SE : status epilepticus. LEV : levetiracetam. LCM : lacosamide

Figure 2:

Use of individual AEDs through time. Results are expressed as percentage of the SE episodes for each year.

AEDs : antiepileptic drugs. SE : status epilepticus. LEV : levetiracetam. CLZ : clonazepam. MDZ : midazolam. PHT : phenytoin. VPA : valproate. LCM : lacosamide. PGB : pregabalin

Figure 3:

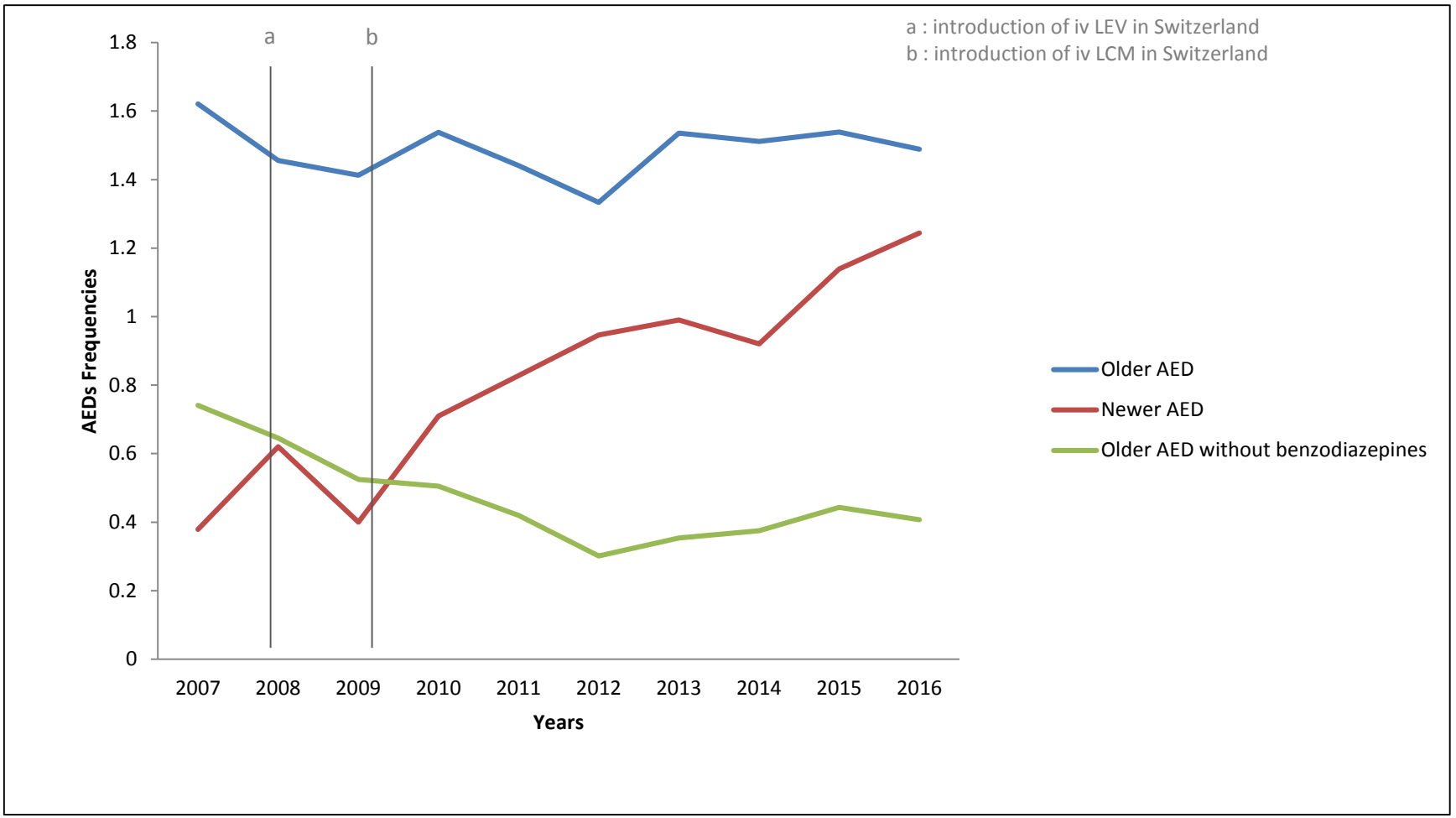
Evolution of mean STESS, refractory SE and intubation for treatment. Results are expressed as percentage of the SE episodes for each year or mean.

AEDs : antiepileptic drugs. SE : Status epilepticus . PRO : propofol. STESS: Status epilepticus severity score. THP : thiopental.

Figure 4 :

Evolution of outcome. Results are expressed as percentage of SE episodes for each year.

SE : Status epilepticus .



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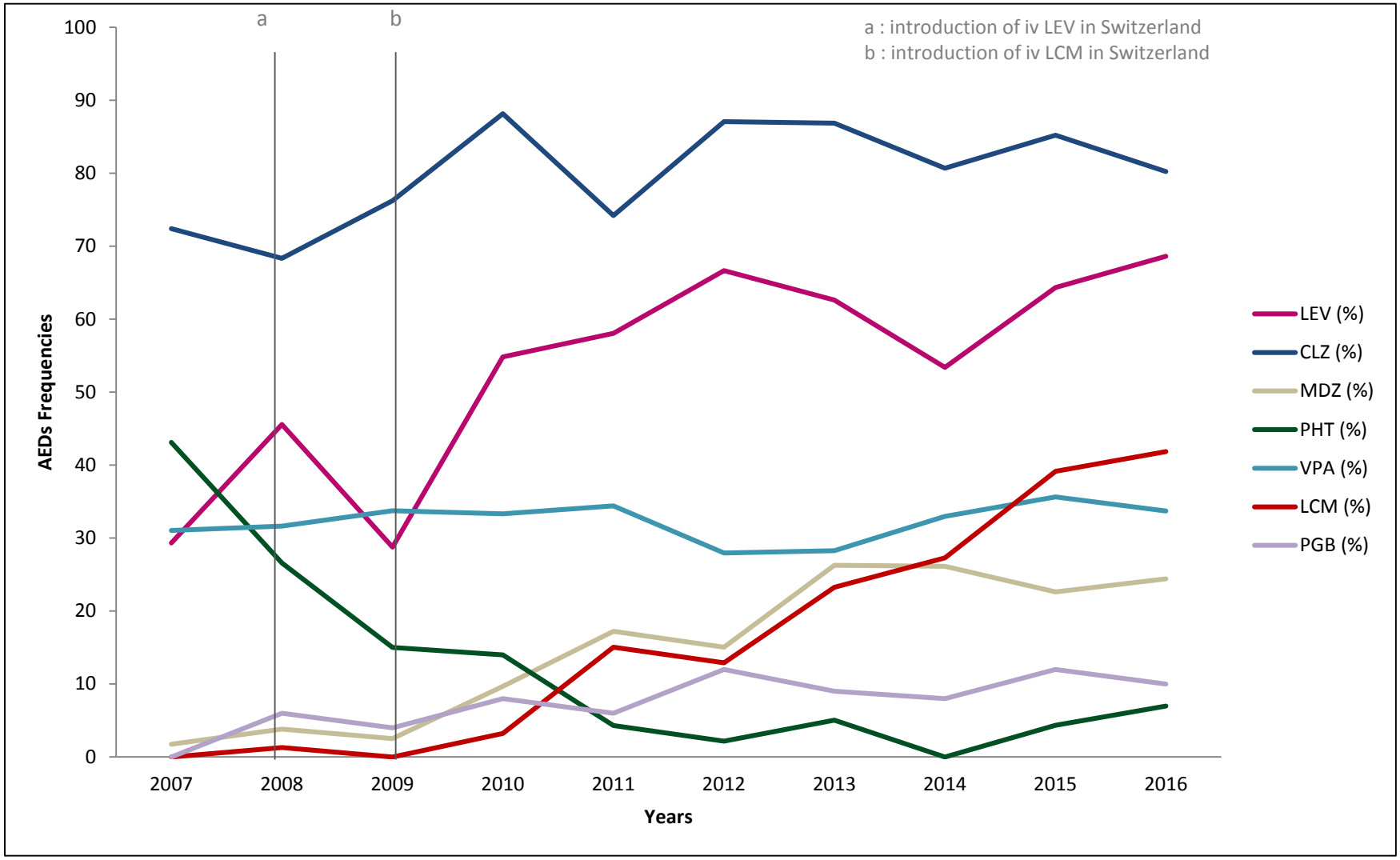

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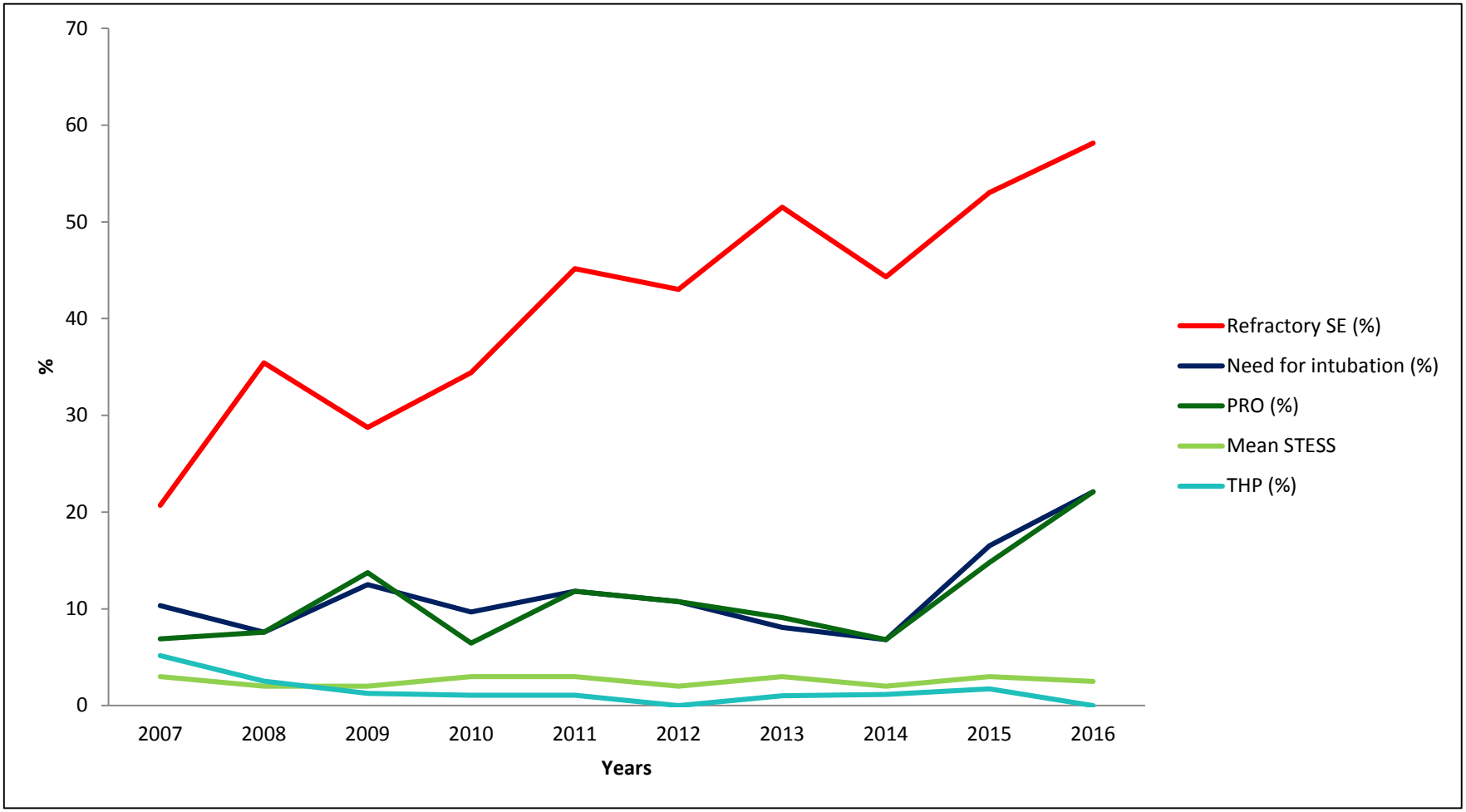

Fig 3. Evolution of mean STESS, refractory SE and intubation for treatment. Results are expressed as percentage of the SE episodes for each year or mean.

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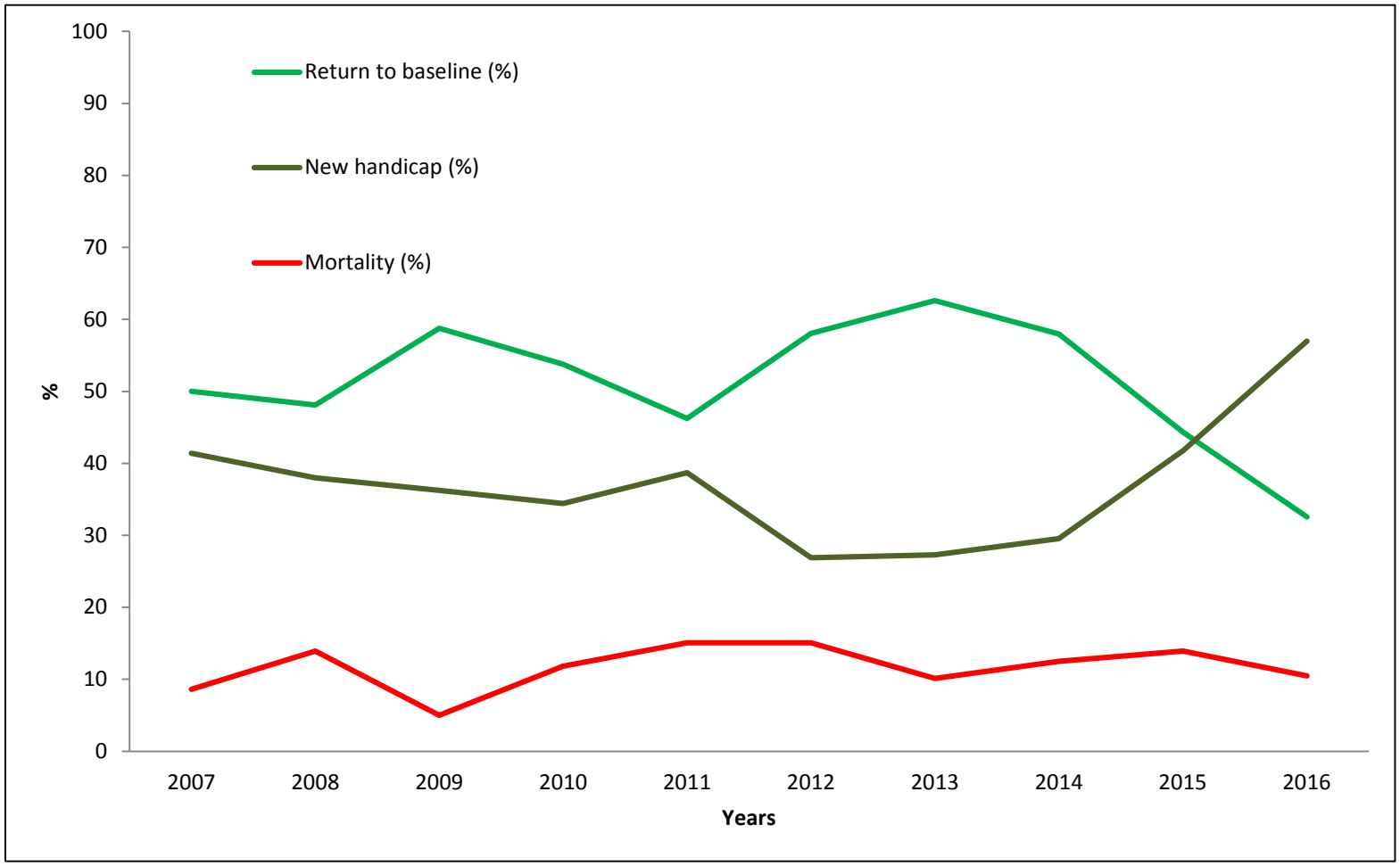

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