Year : 2017

Newer Antiepileptic Drugs in Status Epilepticus: Prescription Trends and Outcome in Comparison with Traditional Agents

Beuchat Isabelle

Beuchat Isabelle, 2017, Newer Antiepileptic Drugs in Status Epilepticus: Prescription Trends and Outcome in Comparison with Traditional Agents

Originally published at : Thesis, University of Lausanne

Posted at the University of Lausanne Open Archive http://serval.unil.ch
Document URN : urn:nbn:ch:serval-BIB_D56908E75C5F1

UNIL | Université de Lausanne
Ecole doctorale

CHUV

UNIVERSITÉ DE LAUSANNE - FACULTÉ DE BIOLOGIE ET DE MÉDECINE
Neuroscience clinique
Neurologie

Newer Antiepileptic Drugs in Status Epilepticus: Prescription Trends and Outcome in Comparison with Traditional Agents

THESE

préparée sous la direction du Professeur Andrea Rossetti

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Isabelle Beuchat

Médecin diplômée de la Confédération Suisse
Originaire de Courtételle (Jura, Suisse)

Lausanne
2017

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Ecole Doctorale
Doctorat en médecine

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Directeur de thèse	*Monsieur le Professeur* ***Andrea Rossetti***
Co-Directeur de thèse	
Expert	*Monsieur le Professeur* ***Armin Von Gunten***
Vice-Directeur de l'Ecole doctorale	*Monsieur le Professeur* ***John Prior***

la Commission MD de l'Ecole doctorale autorise l'impression de la thèse de

Madame Isabelle BEUCHAT

intitulée

Newer Antiepileptic Drugs in Status Epilepticus: Prescription Trends and Outcome in Comparison with Traditional Agents

Lausanne, le 14 novembre 2017

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Résumé

Nouveaux antiépileptiques dans l'état de mal épileptique: évolution de prescription et pronostique en comparaison avec les antiépileptiques traditionnels.

Introduction
Durant les 20 dernières années de nombreux nouveaux antiépileptiques ont été mis sur le marché. Les traitements antiépileptiques sont classiquement divisés en deux groupes ; traditionnel et nouveau, en fonction de leur date de mise sur le marché (avant ou après 1990). Les nouveaux antiépileptiques présentent une meilleure tolérance et moins d'interaction médicamenteuse que les antiépileptiques traditionnels pour une efficacité similaire. Ils sont par conséquent prescrits de plus en plus diffusément. Toutefois peu de données sont disponibles concernant leur utilisation dans l'état de mal ou leur impact sur son pronostique.

Objectifs
- Explorer les changements du pattern de prescription des antiépileptiques dans l'état de mal entre 2007 et 2016, période lors de laquelle plusieurs nouveaux antiépileptiques, y compris avec forme intraveineuse, ont été introduits en Suisse.
- Investiguer l'impact sur le pronostique de l'utilisation de nouveaux antiépileptiques par comparaison aux traditionnels.

Méthode
Nous avons analysé les données d'un registre prospectif contenant les informations sur les états de mal chez les adultes traités au CHUV sur une période de 10ans (2007-2016). La fréquence de prescription annuelle de chaque antiépileptique ainsi du total des antiépileptiques nouveaux et traditionnels (avec et sans inclusion des benzodiazépines) a été calculée. L'association entre l'utilisation d'antiépileptiques nouveaux ou traditionnels avec la mortalité, le retour à l'état de base à la sortie de l'hôpital et les états de mal réfractaires (résistants à deux antiépileptiques y compris benzodiazépines) a ensuite été évaluée.

Résultats
884 épisodes d'état de mal, correspondant à 719 patients ont été étudiés. La prescription d'au moins un nouveau antiépileptique a augmentée de 0.38 par épisode d'état de mal en 2017 à 1.24 par épisode d'état de mal en 2016. Cette augmentation est principalement due à la prescription de levetiracétam et de lacosamide. En parallèle la prescription d'antiépileptiques traditionnels (excluant les benzodiazépines) a diminué à travers le temps passant de 0.74 en 2007 à 0.41 en 2016, corrélant avec la diminution de l'utilisation de phénytoine.
L'utilisation des nouveaux antiépileptiques était indépendamment corrélée avec une probabilité moindre d'un retour à l'état de base à la sortie (OR 0.58, 95% CI 0.40-0.84) et un plus haut risque d'état de mal réfractaire (OR 19.84, 95% CI 12.76-30.84), sans toutefois d'impact sur la mortalité (OR 1.08, 95% CI: 0.58-2.00).

Conclusion
Nous avons observé une augmentation de prescription des nouveaux antiépileptiques dans l'état de mal au cours de la dernière décade. Nos résultats suggèrent un risque possiblement majoré de nouvel handicap à la sortie et d'état de mal réfractaire associé à leur prescription. Dans l'attente d'autres études comparatives, ces résultats pourraient justifier une certaine précaution dans l'utilisation de routine des nouveaux antiépileptiques dans l'état de mal épileptique.

CNS Drugs
DOI 10.1007/s40263-017-0424-1

ORIGINAL RESEARCH ARTICLE

Newer Antiepileptic Drugs in Status Epilepticus: Prescription Trends and Outcomes in Comparison with Traditional Agents

Isabelle Beuchat[1] · Jan Novy[1] · Andrea O. Rossetti[1]

Abstract

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

Objectives The aim of this study was 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 a 10-year period (2007–2016) and assessed the yearly use of newer and traditional AEDs and their association with mortality, return to baseline conditions at discharge, and SE refractoriness, defined as treatment resistance to two AEDs, including benzodiazepines.

Results In 884 SE episodes, corresponding to 719 patients, the prescription of at least one newer AED increased from 0.38 per SE episode in 2007 to 1.24 per SE episode in 2016 (mostly due to the introduction of levetiracetam and lacosamide). Traditional AEDs (excluding benzodiazepines) decreased over time from 0.74 in 2007 to 0.41 in 2016, correlating with the decreasing use of phenytoin. The prescription of newer AEDs was independently associated with a lower chance of return to baseline conditions at discharge (odds ratio [OR] 0.58, 95% confidence interval [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 the prescription of newer AEDs 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 Points

The prescription of newer antiepileptic drugs (AEDs) in status epilepticus (SE) has markedly increased during the last decade, mostly due to the introduction of levetiracetam and lacosamide.

While mortality at hospital discharge did not significantly change, the 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.

1 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

✉ Andrea O. Rossetti
andrea.rossetti@chuv.ch

[1] Service de Neurologie, Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois (CHUV), CHUV-BH07, and Lausanne University Hospital, 1011 Lausanne, Switzerland

Published online: 24 March 2017

[1, 2]. Current SE treatment recommendations are based on a three-step approach, with benzodiazepines as first-line treatment, followed by intravenous antiepileptic drugs (AEDs). If SE termination is not achieved despite the first two lines of therapy, 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 2 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 AEDs, 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 have 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 of AED prescription patterns in SE and its impact on clinical outcome. The aims of this study were to explore the changes in the prescription of newer and traditional AEDs in SE treatment over the last decade, and their association with prognosis.

2 Methods

In this cohort study, we retrospectively analyzed our prospective SE registry recording data on adults with SE episodes treated in our hospital, details of which have been described elsewhere [21, 22]. Briefly, SE was defined as continuous or repetitive seizures, without full recovery in between, lasting more than 30 min (until 2008) and more that 5 min (since 2008) [23]. All patients were identified by the neurological consulting team and the staff of the epilepsy/electroencephalogram (EEG) unit. Children under 16 years of age and subjects with post-anoxic SE were not included. The SE treatment guidelines from our hospital recommend a slow bolus of intravenous clonazepam 0.015 mg/kg, midazolam 0.15 mg/kg (which can also be administered intramuscularly), or lorazepam 0.1 mg/kg as first-line therapy, and intravenous levetiracetam 30 mg/kg, valproate 30 mg/kg, or phenytoin 20 mg/kg, as second-line therapy.

We retrieved data of SE episodes between 1 January 2007 (the first entire year after commencement of the registry) and 31 December 2016, a period encompassing the introduction in Switzerland of several newer intravenous AEDs, such as levetiracetam (2008) and lacosamide (2009). These data included demographics, etiology defined as 'potentially fatal' if potentially leading to death independently of SE treatment [24], the validated Status Epilepticus Severity Score (STESS; relying on age, history of seizures, seizure type, and extent of consciousness impairment prior to treatment) [25], type and number of AEDs prescribed, coma induction for SE treatment, SE refractoriness (defined as the need for 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 into two groups according to the year of marketing (before or after 1990): benzodiazepines, phenobarbital, phenytoin, valproic acid, and carbamazepine were considered 'traditional AEDs', while 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 not introduced in Switzerland until January 2017) were considered 'newer AEDs'. Propofol, thiopental, corticosteroids, ketamine, etomidate, ketogenic diet, emergency surgery, or lack of treatment (spontaneous resolution of the SE episode) were considered separately.

Evolution of the use of both traditional AEDs (including and excluding benzodiazepines, which alone represent 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. The frequency of the prescription of individual AEDs were then reported as a percentage of the SE episodes for each year.

Statistical analysis was performed using Stata version 14 (StataCorp LP, College Station, TX, USA). To test associations with clinical outcome, univariable analyses over the whole study period were performed using the Student's *t* test and Chi-square test, 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 using the Hosmer–Lemeshow test.

3 Results

We recorded 884 SE episodes during the 10-year study period, corresponding to 719 patients. Clinical characteristics are shown in Table 1. The yearly incidence of SE markedly increased during the studied time lapse (from 58

Table 1 Clinical characteristics of the study population

Year	No. of SE episodes	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	60.0	2.3 ± 1.5
2010	93	47.3	62.9 ± 18.7	44.1	43.0	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

SE status epilepticus, *SD* standard deviation, *STESS* Status Epilepticus Severity Score

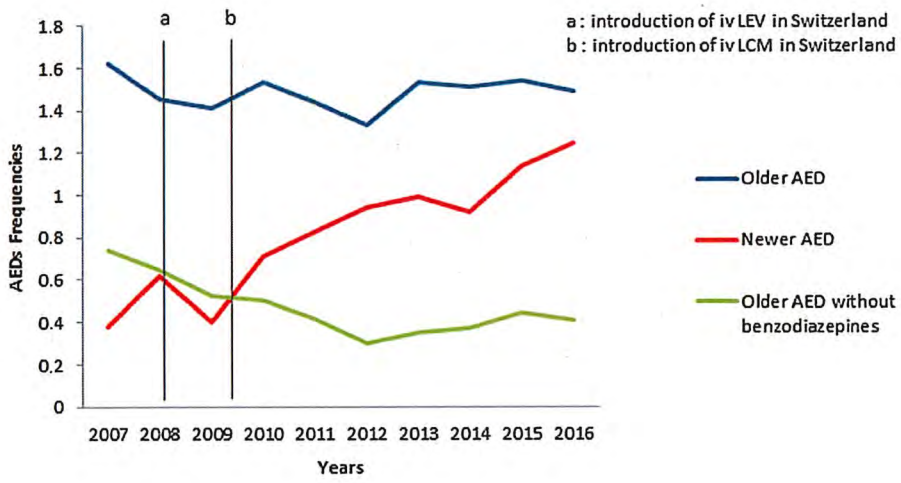

Fig. 1 Evolution of the prescription pattern of newer AEDs, traditional AEDs, and traditional AEDs with exclusion of benzodiazepines. Results are expressed as the yearly ratio between the total number of AEDs prescribed in a given group and the number of SE events. *AEDs* antiepileptic drugs, *SE* status epilepticus, *LEV* levetiracetam, *LCM* lacosamide, *iv* intravenous

episodes in 2007 to 86 episodes in 2016), while the proportions of patients with a 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 Fig. 1, the frequency of use of newer AEDs gradually increased, whereas the utilization of traditional AEDs remained stable over time as a whole, but decreased if benzodiazepines were excluded. Globally, the prescription of at least one newer AED increased from 0.38 per SE episode in 2007 to 1.24 per SE episode in 2016. Conversely, traditional AEDs without benzodiazepines decreased from 0.74 in 2007 to 0.41 in 2016.

The frequency of use of individual AEDs, used in at least 10% of episodes in 1 year, is shown in Fig. 2. Among traditional AEDs, phenytoin showed the most obvious decrease, while the prescription of valproate remained relatively constant. Phenobarbital and carbamazepine were used very rarely (used indeed, respectively, 17 and 8 times). The prescription pattern of benzodiazepines also showed some evolution; clonazepam was most frequently and constantly administered. Lorazepam, diazepam, clobazam and oxazepam were not commonly administered, and their frequency of use decreased slightly. However, the use of midazolam as a first-line agent increased from 0% in 2007 to 15% in 2016, and, as a third-line compound, from 0% in 2007 to 9% in 2016.

Among newer AEDs, levetiracetam and lacosamide showed a major increase in use. In 2007, levetiracetam was used in only 30% of SE episodes, but from 2010, 2 years after the introduction of its intravenous formulation in Switzerland, it was prescribed in more than 50% of SE episodes. Intravenous lacosamide was introduced in Switzerland in 2009, together with the oral form, and, since

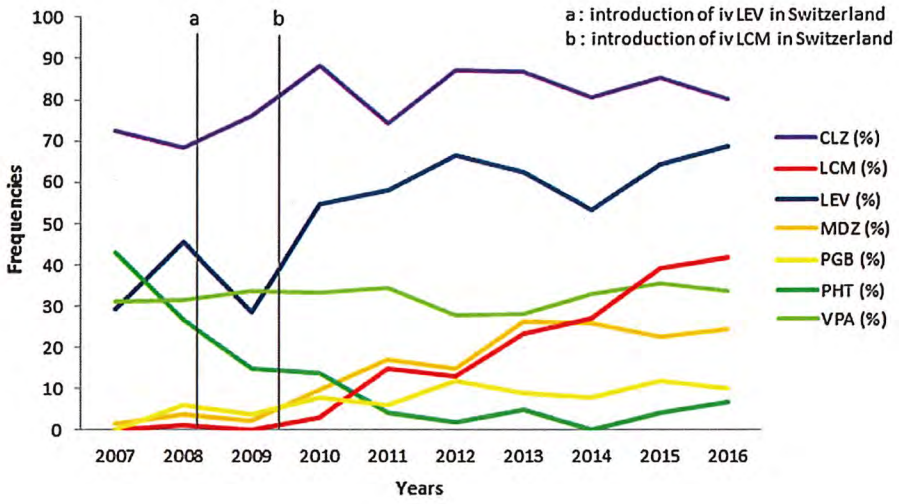

Fig. 2 Use of individual AEDs through time. Results are expressed as a percentage of the SE episodes for each year. *AEDs* antiepileptic drugs, *SE* status epilepticus, *LEV* levetiracetam, *CLZ* clonazepam, *MDZ* midazolam, *PHT* phenytoin, *VPA* valproate, *LCM* lacosamide, *PGB* pregabalin, *iv* intravenous

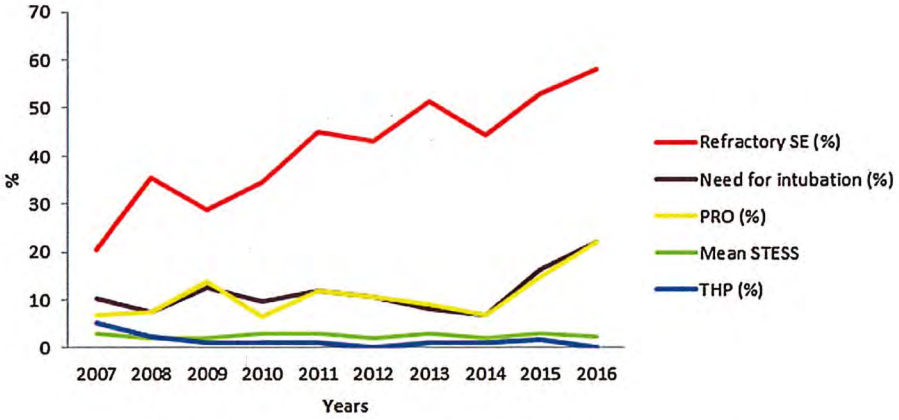

Fig. 3 Evolution of mean STESS, refractory SE and intubation for treatment. Results are expressed as a percentage of the SE episodes for each year or mean. *SE* status epilepticus, *PRO* propofol, *STESS* Status Epilepticus Severity Score, *THP* thiopental

2010, its utilization has gradually increased; it was prescribed in nearly 40% of episodes in 2016. Even if less frequently prescribed, pregabalin use also slightly increased. The use of oxcarbazepine (3 cases), gabapentin (3 cases), lamotrigine (9 cases), topiramate (13 cases), felbamate, retigabine, rufinamide, perampanel, and brivaracetam (1 case each) was almost negligible over the study period.

Among other treatments (Fig. 3), propofol use increased (6.9% [$N = 4/58$] in 2007 vs. 22.1% [$N = 19/86$] in 2016). Further therapeutic approaches, such as thiopental (12 cases), corticosteroids (14 cases), ketamine (6 cases), ketogenic diet (3 cases), surgery (2 cases), and etomidate (1 case) remained extremely rare over the study period. Finally, one to four patients per year did not receive any treatment as their SE episode resolved spontaneously.

The number of refractory SE cases gradually increased through time (Fig. 3), with an average of 2.17 ± 1.98 AEDs prescribed per SE in 2007 and 2.98 ± 1.5 AEDs prescribed in 2016. The mean STESS score slightly increased from 2.5 ± 1.2 in 2007 to 2.7 ± 1.5 in 2016. The need for intubation also increased; in 2007, 10% of patients were treated with pharmacological coma 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 (Fig. 4).

In univariate analyses, potentially fatal etiology, higher STESS score, intubation for SE treatment, SE refractoriness to the first two treatment lines, and newer AED prescriptions 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 univariable and multivariable analyses, adjusted for recognized outcome predictors, especially SE severity (STESS) and etiology. The prescription of newer AEDs was independently correlated to a higher proportion of disabilities at discharge and a higher rate of treatment failures, but not with increased mortality. These three models showed acceptable goodness of fit ($p = 0.33$

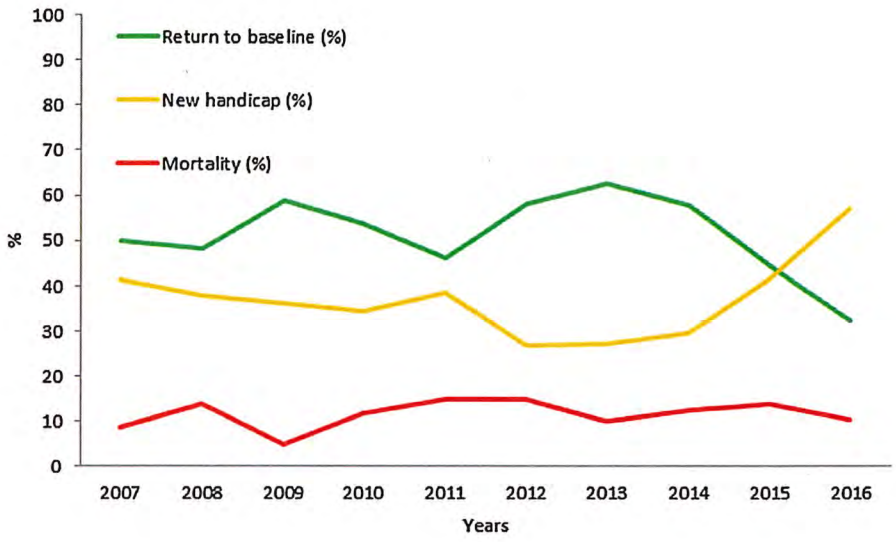

Fig. 4 Evolution of outcome. Results are expressed as a percentage of SE episodes for each year. *SE* status epilepticus

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

	Dead	Alive	Univariate *p* value	Multivariate *p* value	OR	95% CI
No. of patients	106	613				
Female sex (%)	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	Univariate *p* value	Multivariate *p* value	OR	95% CI
No. of episodes	453	431				
Female sex (%)	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	Univariate *p* value	Multivariate *p* value	OR	95% CI
No. of episodes	378	506				
Female sex (%)	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

OR odds ratio, *CI* confidence interval, *STESS* Status Epilepticus Severity Score, *SD* standard deviation, *SE* status epilepticus, *AEDs* antiepileptic drugs

Bold values express significant results

regarding mortality, 0.19 for return to baseline condition, and 0.45 regarding refractoriness).

4 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, the use of newer AEDs was independently associated with higher SE refractoriness and disability at discharge.

A similar trend of increasing prescriptions of newer compounds has already been described, not only in SE but also more generally in patients with epilepsy and in the general population [6–10, 20]. In the present study, this increase was mainly due to the introduction of levetiracetam and lacosamide. Only 2 years after the marketing of intravenous levetiracetam in Switzerland, it became the most frequently used AED in SE in our center, after benzodiazepines. This abrupt rise could, at least in part, be explained by the previous existence of the oral form; physicians may have already been familiar with this agent, generating a shorter adaptation time. Lacosamide became the second most frequently prescribed AED since 2015, 4 years after its marketing.

Regarding traditional AEDs, changes in the prescription of phenytoin mostly accounted for the observed reduction, whereas utilization of valproate remained globally stable. The potential side effects of phenytoin, together with the relatively difficult clinical administration (implying cardiac monitoring) and clinical follow-up (difficult pharmacokinetics and challenging hepatic 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, such as 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 with the present study [20], with a greater likelihood of receiving newer AEDs in patients with more aggressive forms of SE (stratified by potentially fatal etiology, higher STESS, or refractory SE). Indeed, as newer AEDs present fewer cardiorespiratory side effects, a low potential for interactions, and linear pharmacokinetic properties, they could be prescribed preferentially in patients with comedications and significant comorbidities ('confounding by indication'). Nevertheless, our multivariable analysis was adjusted for important outcome predictors, including SE and etiology severities, total number of prescribed AEDs, and SE refractoriness.

Finally, the number of SE episodes in our center almost doubled between 2007 and 2016, possibly due to the increase in 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, which 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. However, the increase in the proportion of patients with a new disability at discharge seems 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 the addition of levetiracetam to clonazepam [33].

Levetiracetam was by far the most frequently used newer AED. Various studies, including a meta-analysis, comparing levetiracetam with phenytoin or valproate, showed no difference in terms of clinical seizure 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 prescriptions with or without 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 h to achieve maximum concentrations in the cerebrospinal or brain extracerebral fluid [35–37]. On the other hand, animal studies with phenytoin show maximum concentrations in cerebrospinal and brain extracerebral fluids within 9–13 min and 39–34 min, respectively [38]. This could possibly correlate with a slower clinical action of levetiracetam and at least partially explain the relationship between refractoriness and newer AEDs.

To the best of our knowledge, our study is the first to analyze prescription patterns of AEDs in SE over a long time period in a large, well-characterized, adult cohort. With the SE registry being prospectively filled by the same

investigators, its internal validity appears robust. Nevertheless, we acknowledge limitations. We assessed only the prescription of AEDs, without information relating to treatment side effects. Furthermore, we aimed to describe 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, the 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 consideration of robust outcome predictors (etiology, STESS score) over a more restricted time lapse [39]. It also seems 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 disabilities, which evolve over time. While a systematic bias seems unlikely, we underscore that mortality, being a robust variable, did not correlate with newer AED prescriptions. In any case, these considerations do not apply to SE refractoriness. The definition of SE timing changed in 2008; however, we extrapolate that this may have led us to miss, at most, only seven episodes lasting less than 30 min in 2007 (corresponding to less than 1% of the total number). Finally, due to the study design, the described associations do not necessarily reflect causality.

5 Conclusion

A growing trend in newer AED prescriptions in SE has been observed over the last decade. However, our findings do not show a resulting improvement in prognosis, but rather they seem to suggest an association with increased new disabilities at discharge, as well as 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 in elucidating this issue.

Acknowledgements The authors thank Christine Stähli, RN, and the EEG technologists and fellows for help in data acquisition.

Compliance with Ethical Standards

Funding None.

Conflict of interest Isabelle Beuchat, Jan Novy and Andrea Rossetti declare no conflicts of interest with regard to the findings reported in this study.

References

1. Claassen J, Riviello JJ, Silbergleit R. Emergency neurological life support: status epilepticus. Neurocrit Care. 2015;23(Suppl 2):S136–42.
2. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.
3. Meierkord H, Boon P, Engelsen B, Göcke K, Shorvon S, Tinuper P, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17(3):348–55.
4. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16(1):48–61.
5. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54(3):551–63.
6. de Groot MCH, Schuerch M, de Vries F, Hesse U, Oliva B, Gil M, et al. Antiepileptic drug use in seven electronic health record databases in Europe: a methodologic comparison. Epilepsia. 2014;55(5):666–73.
7. Landmark CJ, Fossmark H, Larsson PG, Rytter E, Johannessen SI. Prescription patterns of antiepileptic drugs in patients with epilepsy in a nation-wide population. Epilepsy Res. 2011;95(1–2):51–9.
8. Berman E, Marom E, Ekstein D, Blatt I, Eyal S. Utilization of antiepileptic drugs in Israel. Epilepsy Behav. 2016;61:82–5.
9. Italiano D, Capuano A, Alibrandi A, Ferrara R, Cannata A, Trifirò G, et al. Indications of newer and older anti-epileptic drug use: findings from a southern Italian general practice setting from 2005–2011. Br J Clin Pharmacol. 2015;79(6):1010–9.
10. Savica R, Beghi E, Mazzaglia G, Innocenti F, Brignoli O, Cricelli C, et al. Prescribing patterns of antiepileptic drugs in Italy: a nationwide population-based study in the years 2000–2005. Eur J Neurol. 2007;14(12):1317–21.
11. Novy J, Rossetti AO. Oral pregabalin as an add-on treatment for status epilepticus. Epilepsia. 2010;51(10):2207–10.
12. Madžar D, Kuramatsu JB, Gerner ST, Huttner HB. Assessing the value of topiramate in refractory status epilepticus. Seizure. 2016;38:7–10.
13. Santamarina E, Toledo M, Sueiras M, Raspall M, Ailouti N, Lainez E, et al. Usefulness of intravenous lacosamide in status epilepticus. J Neurol. 2013;260(12):3122–8.
14. Kellinghaus C, Berning S, Immisch I, Larch J, Rosenow F, Rossetti AO, et al. Intravenous lacosamide for treatment of status epilepticus. Acta Neurol Scand. 2011;123(2):137–41.
15. Knake S, Gruener J, Hattemer K, Klein KM, Bauer S, Oertel WH, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. J Neurol Neurosurg Psychiatry. 2008;79(5):588–9.
16. Rüegg S, Naegelin Y, Hardmeier M, Winkler DT, Marsch S, Fuhr P. Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. Epilepsy Behav. 2008;12(3):477–80.
17. Chakravarthi S, Goyal MK, Modi M, Bhalla A, Singh P. Levetiracetam versus phenytoin in management of status epilepticus. J Clin Neurosci. 2015;22(6):959–63.

18. Alvarez V, Januel J-M, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia. 2011;52(7):1292–6.
19. Brigo F, Bragazzi N, Nardone R, Trinka E. Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilepticus. Epilepsy Behav. 2016;64 (Part A):110–5.
20. Jaques L, Rossetti AO. Newer antiepileptic drugs in the treatment of status epilepticus: impact on prognosis. Epilepsy Behav. 2012;24(1):70–3.
21. Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. Epilepsia. 2010;51(2):251–6.
22. Marchi NA, Novy J, Faouzi M, Stähli C, Burnand B, Rossetti AO. Status epilepticus: impact of therapeutic coma on outcome. Crit Care Med. 2015;43(5):1003–9.
23. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(1):120–2.
24. Rossetti AO, Hurwitz S, Logroscino G, Bromfield EB. Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation. J Neurol Neurosurg Psychiatry. 2006;77(5):611–5.
25. Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol. 2008;255(10):1561–6.
26. Redecker J, Wittstock M, Benecke R, Rösche J. Comparison of the effectiveness of four antiepileptic drugs in the treatment of status epilepticus according to four different efficacy criteria. Epilepsy Behav. 2015;49:351–3.
27. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet. 2007;369(9566):1000–15.
28. Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet. 2007;369(9566):1016–26.
29. Vazquez B. Monotherapy in epilepsy: role of the newer antiepileptic drugs. Arch Neurol. 2004;61(9):1361–5.
30. Kwan P, Brodie MJ. Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. Neurology. 2003;60(11 Suppl 4):S2–12.
31. Ney JP, van der Goes DN, Nuwer MR, Nelson L, Eccher MA. Continuous and routine EEG in intensive care: utilization and outcomes, United States 2005–2009. Neurology. 2013;81(23):2002–8.
32. Betjemann JP, Josephson SA, Lowenstein DH, Burke JF. Trends in status epilepticus-related hospitalizations and mortality: redefined in US practice over time. JAMA Neurol. 2015;72(6):650–5.
33. Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol. 2016;15(1):47–55.
34. Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia. 2015;56(8):1275–85.
35. Tong X, Patsalos PN. A microdialysis study of the novel antiepileptic drug levetiracetam: extracellular pharmacokinetics and effect on taurine in rat brain. Br J Pharmacol. 2001;133(6):867–74.
36. Nicolas J-M, Hannestad J, Holden D, Kervyn S, Nabulsi N, Tytgat D, et al. Brivaracetam, a selective high-affinity synaptic vesicle protein 2A (SV2A) ligand with preclinical evidence of high brain permeability and fast onset of action. Epilepsia. 2016;57(2):201–9.
37. Doheny HC, Ratnaraj N, Whittington MA, Jefferys JG, Patsalos PN. Blood and cerebrospinal fluid pharmacokinetics of the novel anticonvulsant levetiracetam (ucb L059) in the rat. Epilepsy Res. 1999;34(2–3):161–8.
38. Wang X, Patsalos PN. A comparison of central brain (cerebrospinal and extracellular fluids) and peripheral blood kinetics of phenytoin after intravenous phenytoin and fosphenytoin. Seizure. 2003;12(6):330–6.
39. Rossetti AO, Alvarez V, Januel J-M, Burnand B. Treatment deviating from guidelines does not influence status epilepticus prognosis. J Neurol. 2013;260(2):421–8.
40. Bleck T, Cock H, Chamberlain J, Cloyd J, Connor J, Elm J, et al. The Established Status Epilepticus Trial 2013. Epilepsia. 2013;54(Suppl 6):89–92.