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# **Newer antiepileptic drugs in the treatment of status epilepticus: impact on prognosis**

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# **Newer antiepileptic drugs in the treatment of status epilepticus: impact on prognosis**

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## Summary

Background: Newer antiepileptic drugs (AED) are increasingly prescribed, and seem to have a comparable efficacy as the classical AED, but are better tolerated. Very scarce data exist regarding their prognostic impact in patients with status epilepticus (SE). We therefore analyzed the evolution of prescription of newer AED between 2006-2010 in our prospective SE database, and assessed their impact on SE prognosis.

Methods: We found 327 SE episodes occurring in 271 adults. The use of older versus newer AED (levetiracetam, pregabalin, topiramate, lacosamide) and its relationship to outcome (return to clinical baseline conditions, new handicap, or death) were analyzed. Logistic regression models were applied to adjust for known SE outcome predictors.

Results: We observed an increasing prescription of newer AED over time (30% of patients received them at the study beginning, vs. 42% towards the end). In univariate analyses, patients treated with newer AED had worse outcome than those treated with classical AED only (19% vs 9% for mortality; 33% vs 64% for return to baseline,  $p < 0.001$ ). After adjustment for etiology and SE severity, use of newer AED was independently related to a reduced likelihood of return to baseline ( $p < 0.001$ ), but not to increased mortality.

Conclusion: This retrospective study shows an increase of the use of newer AED for SE treatment, but does not suggest an improved prognosis following their prescription. Also in view of their higher price, well-designed, prospective assessments analyzing their impact on efficacy and tolerability should be conducted before a widespread use in SE.

Keywords: levetiracetam, topiramate, pregabalin, lacosamide, outcome, mortality

Status epilepticus (SE) represents a common neurological emergency that is associated with significant mortality and morbidity (Lowenstein, 1999), and thus requires a prompt management to avoid neurological sequelae or death (Lowenstein & Alldredge, 1998; Shorvon, 2001).

Current SE treatment protocols advocate a three-step approach, with benzodiazepines as initial therapy followed by the use of antiepileptic drugs (AED) administered intravenously (Meierkord et al., 2010). When SE is refractory to the two first treatment lines, a coma induction with an anaesthetic agent may be necessary (Lowenstein, 1998; Meierkord et al., 2010). Newer AED have been increasingly marketed since about two decades; globally, efficacy seems unchanged as compared to traditional AED, but they are generally better tolerated (Kwan & Brodie, 2003). These compounds are increasingly prescribed, although indications other than epilepsy seem to contribute to this trend (Alacqua et al., 2009). Newer AED have been used in the treatment of SE in the last years, both in oral (Towne et al., 2003; Rossetti & Bromfield, 2006; Novy & Rossetti, 2010; Stojanova & Rossetti, 2011), and intravenous forms (Berning et al., 2009; Rüegg et al., 2008; Knake et al., 2008; Kellinghaus et al., 2011). It remains however unclear if the use of newer AED has led to an improved prognosis in patients suffering from SE, and whether they are increasingly used in this setting.

The aim of this study was to describe the evolution of prescription of newer AED in SE treatment over the years 2006–2010 in our hospital, and to investigate their impact on SE prognosis.

## **Methods**

### **Database, patients, SE definition**

Our prospective SE database (Novy & Rossetti, 2010) that identifies adults with SE episodes admitted to our center (a University hospital) was retrospectively analysed for this study; the period considered spans between April 1, 2006 and September 30, 2010. Patients were identified by 2 epileptologists and the neurologic consulting team; EEG were systematically performed for every patient with a suspicion of SE. Status epilepticus was considered as an epileptic seizure lasting more than 30 minutes, or several epileptic seizures without return to

baseline between seizures. Patients under 16 years and episodes of post-anoxic SE were not included due to markedly different prognostic implications.

### **Definition of variables**

Age, gender, history of previous seizures, seizure types (partial vs. generalized), level of consciousness, SE duration, time to treatment, treatment type and etiology of SE were prospectively identified. Older age, extent of consciousness impairment, and acute symptomatic etiology have been consistently shown to be independently related to poor outcome following SE (Logroscino et al., 1997; Towne et al., 1994; Chin et al., 2004; Claassen and al., 2002; Schneker & Fountain, 2003; Rossetti et al., 2006); the SE severity score (STESS), a validated clinical prognostic tool considering age, seizure type, consciousness impairment, and history of previous seizures (as etiology surrogate), was prospectively calculated for each patient on admission and dichotomized in the database as  $<3$  (favourable) or  $\geq 3$  (unfavourable) (Rossetti et al., 2008). Etiology was considered as “potentially fatal”, in analogy to previous works, if leading to death without an appropriate treatment independently of SE (Rossetti et al., 2006; Novy et al., 2010). These etiologies include for example: massive ischemic and hemorrhagic stroke, primary or secondary cerebral tumor, central nervous system (CNS) infection, severe autoimmune disease, AIDS with CNS complication, and metabolic disturbance sufficient to cause coma, eclampsia, and sepsis.

Use of AED for SE treatment was prospectively recorded in the database; for the purpose of this analysis, topiramate, levetiracetam, pregabalin and lacosamide were considered as newer AEDs ; in fact, other newer AED (such as lamotrigine, gabapentine, felbamate, vigabatrine, tiagabine, oxcarbazepine, or retigabine) were practically never used in a SE setting in our hospital. Classical AED mainly used in SE in our database are phenytoin, valproate, barbiturates, and benzodiazapines. SE episodes were dichotomized into those with at least one newer AED (irrespective of the medication) or not. Outcome at hospital discharge was prospectively categorized as return to baseline clinical conditions, disabled (i.e., presence of a new handicap), or death.

### **Statistical analysis**

The prevalence of use of newer AED, and clinical prognosis, were first described according to two periods, defined by the availability of intravenous formulations of levetiracetam and

lacosamide in our hospital (April 1, 2006 to September 30, 2007; October 1, 2007 to September 30, 2010). Subsequently, we analyzed outcome distribution according to the use of newer AED, and robust SE outcome predictors (etiology, STESS). Frequency tables were assessed using  $\chi^2$  tests. Finally, stepwise multivariable logistic regressions were used to evaluate the impact of use of newer AED on prognosis, adjusting for other predictors; models were evaluated with the Hosmer-Lemeshow test. All calculations were performed with the version 9 of the Stata software (College Station, TX, USA); significance was considered at  $p < 0.05$ .

## Results

We identified 327 SE episodes occurring in 271 patients during the 54-months study period. Mean age was 60 years (SD  $\pm$  18.3). There were 176 women (53.8%); 40 patients (14.8%) presented more than one SE episode. Over the 5-year period, 128 SE episodes (39.2%) were treated with at least one of the newer AED, 70 of them were women (54.7%), and mean age in this group was 59 years (SD  $\pm$ 16.7; range 16-92). We observed a trend favouring the use of newer AED during the second period of time (102 episodes, 42.2%) over the first one (26 episodes, 30.6%) ( $p=0.060$ ) (Table 1).

Prognosis according to the two chronological periods showed non-significant differences, with a slightly higher mortality in the earlier period ( $p=0.303$ ) (Table 2). However, in univariable analyses, patients treated with newer AED had a worse outcome than patients receiving only classical AED during the entire study period (Table 3).

In the studied cohort, patients with a potentially fatal etiology were more often treated with newer AED. There was also a trend to treat patients with a high STESS ( $\geq 3-6$ ) more often with newer AED (Table 4). After adjustment for potentially fatal etiology and SE severity score (that included age, seizure semiology, extent of consciousness impairment, and history of previous seizures), use of newer AED was significantly related to a higher risk of lack of return to baseline clinical conditions at discharge, but not to increased mortality. Both models showed an acceptable goodness of fit, and confirmed the robustness of STESS and etiology as independent outcome predictors (Table 5).

## Discussion

This study focusing on the prescription of newer AED in patients with SE shows that their use tended to increase over the past 5 years. Moreover, treatment of SE with newer AED was associated with increased disability at hospital discharge, but not higher mortality.

A similar trend of increased prescription of newer AED has been already shown in recent studies (Alacqua et al., 2009; Savica et al., 2007); although that seemed to at least partly reflected extra-epileptic indications (e.g., neuropathic pain), other studies demonstrate that newer AED are increasingly used in patients with epilepsy (Pugh et al., 2008); however, the speed of this rise appears relatively modest (Hsia et al., 2010). To the best of our knowledge, a similar analysis has not been yet performed in patients with SE, and confirms the global trend.

In univariable analyses, patients who only received classical AED had a more favorable prognosis than those who also received newer AED ( $p < 0.001$ ). This differs from previous assessments on patients with epilepsy, which globally showed similar efficacy with fewer side effects for the newer AED (Beydoun, 1997; Kwan & Brodie, 2003; Vasquez, 2004; Marson et al., 2007), and may reflect some confounding in our cohort. In fact, consideration of known SE outcome predictors discloses that patients with a potentially fatal etiology (Rossetti et al., 2006; Tsai et al., 2009) had received newer AED more often for the treatment of their SE episode ( $p = 0.001$ ); furthermore, subjects with a high STESS ( $\geq 3$ ) (Rossetti et al., 2008) also tended to show a higher chance to be treated with newer AED ( $p = 0.057$ ). These two variables thus may explain at least in part the results: patients with SE forms felt to be more aggressive had a greater likelihood to receive further compounds of the therapeutic arsenal, including newer AED; this is highlighted by the multivariable analysis: after correction for etiology and SE severity, only disability, but not mortality, resulted independently related to the use of newer AED. A recent study analysing the same database showed a higher rate of SE treatment failure with levetiracetam than with valproate but no impact on the outcome at hospital discharge (Alvarez et al., 2011). A possible explanation for these results could be that dosages of levetiracetam used in our hospital, between 1000-3000 mg daily, were somewhat lower than those recently recommended in the literature (3,000-3,500 mg daily) (Berning et al., 2009; Trinka & Dobesberger, 2009; Shorvon, 2011; Swisher et al., 2011).

While a greater risk of disability after use of newer AED could theoretically reflect some reduced efficacy of these compounds, an information bias may also exist regarding the outcome. Indeed, the “return to baseline” clinical conditions may depend on the moment it was assessed, as disability may evolve over time, as opposed to mortality that represents a more “robust” outcome. In our database, outcome was scored at hospital discharge, a variable time frame. In fact, mortality was not different among users of newer and classical AED only, and the different likelihood of return to baseline may simply reflect the need for a longer convalescence after a severe SE episode, even after consideration of two solid SE predictors. Our study has some other potential limitations. A selection bias may exist because it considers only patients from a university hospital; however, most SE patients are treated in institutions with availability of ICU and neurologists. Due to its retrospective design, the analysis does not allow us to know whether patients were already receiving the assessed treatments before admission, or if these were initiated de novo at hospital during the seizure. Finally, we had no information about treatment side-effects.

In conclusion, despite some increase in the prescription of newer AED for SE treatment over the past few years, this study does not support an improved prognosis following their prescription, if considered as a group, and corroborates the aforementioned finding on the lack of superiority of levetiracetam as compared to valproate or phenytoin (Alvarez et al, 2011). Since newer AED are more expensive than classical ones, the marketing efforts aimed at their increased use in SE should rely on well-designed, prospective assessments showing their superiority (at least regarding side effects). Such studies would be of great importance in this clinical setting (Shorvon & Ferlisi, 2011; Rossetti & Lowenstein, 2011).

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**Table 1.** Treatment of SE episodes stratified according to two periods of time.

	Classical AED only	Newer AED	p-value (test)
April 2006- September 2007	59 (69.41%)	26 (30.59%)	0.060 ( $\chi^2$ )
October 2007- September 2010	140 (57.85%)	102 (42.15%)	

**Table 2.** Prognosis according to two periods of time.

	Return to baseline	Disabled	Dead	p-value
April 2006- September 2007	42 (49.41%)	28 (32.94%)	15 (17.65%)	0.303 ( $\chi^2$ )
October 2007- September 2010	127 (52.48%)	88 (36.36%)	27 (11.16%)	

**Table 3.** Prognosis regarding to the medication in the whole study period

04 2006 – 09 2010	Return to baseline	Disabled	Dead	p-value
Classical AED only	127 (63.81%)	54 (27.14%)	18 (9.04%)	<0.001 ( $\chi^2$ )
Newer AED	42 (32.81%)	62 (48.43%)	24 (18.75%)	

**Table 4.** Prevalence of potential fatal etiology and STESS (status epilepticus severity score) regarding to the use of medication in the whole study period

	No pot. fatal etiology	Pot. fatal etiology	STESS 0-2	STESS 3-6
Classical AED only	129 (64.82%)	70 (35.18%)	107 (53.77%)	92 (46.23%)
Newer AED	59 (46.1%)	69 (53.9%)	55 (42.97%)	73 (57.03%)
p-value	0.001 ( $\chi^2$ )		0.057 ( $\chi^2$ )	

**Table 5.** Multivariable logistic regression models using risk of lack to return to baseline clinical conditions at hospital discharge, or mortality, as outcome. Results are given as OR (95% CI).

	Lack of return to baseline	Mortality
Use of newer AED	3.23 (1.88 – 5.52), p<0.001	1.60 (0.80 -3.21), p=0.18
STESS 3-6	4.08 (2.42 – 6.89), p<0.001	4.11 (1.80- 9.38), p<0.001
Potentially fatal etiology	5.14 (3.03 – 8.73), p<0.001	4.32 (2.00 – 9.33), p<0.001
Goodnes of fit ( $\chi^2$ )	0.23	0.60

AED = antiepileptic drugs; STESS = Status Epilepticus Severity Score