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The impact of first response to out-of-hospital status epilepticus

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Background: In patients with status epilepticus (SE), pre-hospital response by emergency medical services (EMS) seems crucial for favourable course and outcome, but studies in this context are scarce.
We sought to determine the impact of EMS response to out-of-hospital SE on outcome.

Methods: From 2005-2014, clinical EMS and in-hospital data were assessed in consecutive adult patients admitted to an academic medical center with out-of-hospital SE.

Results: Among 213 SE patients, 150 were admitted via the EMS. SE was confirmed within a mean of 199 minutes after admission and missed by the EMS in 55%, foremost in patents with increased age ($p<0.001$), a higher median Glasgow Coma Score (GCS) ($p=0.013$), without seizure history ($p<0.001$), and with acute/fatal etiologies ($p=0.002$). Patients with missed epileptic events were less likely to receive benzodiazepines before admission ($p=<0.001$). Multivariable analysis uncovered that patents with missed epileptic events had increased odds for no return to functional baseline in survivors until discharge (OR=2.9; 95%CI 1.2-7.2; $p=0.020$) independent of age, acute/fatal etiology, GCS, Charlson Comorbidity Index, and SE duration. According to the multivariable model, missed epileptic event was more likely with older age, higher GCS and no seizure history. The area under the receiver operating characteristic curve for prediction of missed epileptic event by these variables was 0.818.

Conclusions: Out-of-hospital SE is missed especially in patients with increasing age, high initial GCS, and no seizure history. This calls for heightened awareness for SE in such patients, as missed epileptic events are associated with inappropriate treatment and increased odds for no return to functional baseline in survivors independent of established outcome predictors.

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Phase I study to determine the pharmacokinetics, pharmacodynamics, and safety of IV ganaxolone in healthy adults

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Background: Ganaxolone (GNX), a synthetic analog endogenous allopregnanolone, is in development for treatment of epilepsy and other neurological and psychiatric conditions. GNX allosterically modulates γ-aminobutyric acid type A (GABAA) receptors and has sedative, anxiolytic and anticonvulsant effects. GNX IV is being developed to expand treatment options for patients with status epilepticus. The objective of this study was to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of GNX IV administered as a bolus dose and continuous infusion to healthy participants.

Methods: This was a single site, sequential cohort evaluation of GNX IV. The study consisted of 6 cohorts. PK, changes in EEG, BIS, and sedation scores, and safety (ECG, vital signs, physical examination findings, and adverse events) were assessed following a single bolus and bolus dosing followed by continuous infusion of GNX IV. The PK from each cohort was modeled to select the doses for subsequent cohorts. One cohort had an objective to explore the sedative effects of ganaxolone, including the potential of the drug to induce burst suppression

Results: Thirty-six subjects received study drug and 35 subjects completed the initial 5 cohorts. Treatment emergent adverse events were mild in severity and

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resolved without intervention. There were no clinically significant changes in physical exams, vital signs, ECGs, and laboratory values. Changes in BIS and sedation scores were evident within 5-15 minutes of infusion start and the majority returned to baseline within 30 minutes post bolus dose. GNX concentrations in plasma were generally proportional to the administered dose. Potential anti-convulsant plasma concentrations were achievable with a bolus dose. After the IV bolus dose or cessation of the IV infusion dose, concentrations of GNX in plasma declined in a multi-phasic manner.

Conclusions: GNX administered as a rapid IV bolus or bolus with continuous infusion was generally safe and well tolerated; there were no safety issues that limit getting to a potentially efficacious plasma concentration in a short period of time. BIS and qualitative EEG changes correlated with expected GABAA mechanism of action. Predictable PK from this study enables dosing guidance for GNX IV.

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Status epilepticus as a manifestation of paradoxical aggravation by treatment with newer-generation antiepileptic drugs

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Background: Seizure aggravation by antiepileptic drugs (AEDs) is defined as a paradoxical reaction when an AED increases the frequency and/or severity, and/or changes the pattern of a seizure type against it is usually effective, or when it leads to the onset of new types of seizures, or the occurrence of status epilepticus (SE). The purpose of our study is to report cases with SE caused by treatment with some of the newer-generation AEDs.

Methods: The study was performed with the participation of 1259 consecutive patients with epilepsy who attended the Clinic of Neurology at the University Hospital in Plovdiv, Bulgaria for a regular examination or in cases of unsatisfactory seizure control or adverse events from treatment. In 324 patients the antiepileptic treatment included some of the newer-generation AEDs. The data about epilepsy, antiepileptic treatment and its effect on seizure frequency and severity were collected through an interview, examination of the patients' medical documentation and a prospective study of all participants for at least 6 months from the initiation of a newer-generation AED.

Results: SE as a manifestation of paradoxical aggravation by newer-generation AEDs was reported in 5 (1.54%) patients with refractory epilepsy (4 women, mean age of 34 years). In a male participant with focal epilepsy convulsive SE was reported 11 days after an increased dose of oxcarbazepine (1800 mg/d) and topiramate (200 mg/d). In 2 patients with focal/generalized epilepsy the treatment with levetiracetam 3000/2000 mg/d induced seizure aggravation and convulsive SE in the following 1-5 months. In 1 patient with focal epilepsy the treatment with pregabalin 225 mg/d induced focal convulsive SE in 1 week. In 1 patient with focal epilepsy the dose increase of lacosamide from 200 to 300 mg/d caused seizure aggravation and convulsive SE in 1 month. In all cases adaptation of therapy resulted in seizure improvement.

Conclusions: Despite the low frequency of SE as a manifestation of seizure aggravation, newer-generation AEDs may have also the potential of causing it. This necessitates timely focusing of attention on effects from treatment with the purpose of prevention of serious complications.

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Characterization of allopregnanolone pharmacokinetics in dogs with naturally-occurring epilepsy to support use in the initial treatment of status epilepticus

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