

## **Title: Randomized Trial of Three Anticonvulsants Medications for Status Epilepticus**

Authors: Jaideep Kapur, M.B., B.S., Ph.D., Jordan Elm, Ph.D., James M. Chamberlain, M.D., William Barsan, M.D., James Cloyd, Pharm.D., Daniel Lowenstein, M.D., Shlomo Shinnar, M.D., Ph.D., Robin Conwit, M.D., Caitlyn Meinzer, Ph.D., Hannah Cock, M.D., Nathan Fountain, M.D., Jason T. Connor, Ph.D., and Robert Silbergleit, M.D., for the NETT and PECARN Investigators

Journal Title: The New England Journal of Medicine

Date, issue, pages of publication: November 28th 2019, 381:2103 - 13. DOI: 10.1056/NEJMoa1905795

### Introduction:

This randomised, blinded, adaptive trial was performed to provide the first experimental data to support antiepileptic drug (AED) choice in benzodiazepine - resistant generalised convulsive status epilepticus (GCSE). It compared the efficacy & safety of levetiracetam, fosphenytoin and valproate in patients in whom benzodiazepines had failed to terminate GCSE in 400 patients across 57 emergency departments across the United States over a period of two years.

The study was halted at interim analysis as there was <1% probability of significance in the primary efficacy endpoint: the absence of clinically apparent seizure activity & improving responsiveness at 60 minutes.

### Patient Eligibility:

Patients >2 years old with GCSE resistant to a 'generally accepted' dose of benzodiazepine with persistent or recurrent seizure activity within 5 - 30 minutes after last benzodiazepine administration. Exclusion criteria included seizure activity provoked by hypoglycaemia, trauma etc.; pregnancy; incarceration or severe renal or hepatic disease.

### Conclusion:

There was no significant difference identified between levetiracetam, fosphenytoin or valproate in efficacy or safety in the treatment on benzodiazepine - resistant GCSE.

### Study Critique:

The importance of this study is that it provided much - needed experimental data for AED choice in benzodiazepine - resistant convulsive status. Prior to this, the evidence informing this choice was observational (1)(2) & suggested that valproate was most efficacious, a finding not duplicated in this experimental data. The accuracy of this study was maximised with the innovative use of a protocol assist device which diminished protocol deviations & maximised enrolment. A further strength were the broad eligibility criteria employed: overly stringent criteria would limit enrolment in this emergency situation and the real - world applicability of the findings. ⅔ enrolled had a history of epilepsy, and they were evenly distributed between treatment arms. However data on these patients' antiepileptic maintenance treatment was considered during randomisation and the effect of maintenance AED therapy on

treatment response was not reported. This important confounder was not accounted for and represents a significant limitation.

Further limitations include the enrolment of 37 patients with non-epileptic seizures; the lack of EEG use to determine seizure cessation; dose capping of fosphenytoin due to standardisation of infusion times to allow blinding; and data collection for only 24h post enrolment.

#### Study Impact & Future Directions:

This study could potentially significantly impact management of GCSE in Ireland. There are no Irish national guidelines on the management of GCSE, and this publication could form a basis for their development, aiding standardisation and optimisation of care across the country. It lends weight to the 2016 American Epilepsy Society Guideline (3) which equally promotes the use of levetiracetam, fosphenytoin and valproic acid, over the 2012 NICE guideline (4) which recommends either phenytoin or phenobarbital in this scenario. This study has prompted me to begin a retrospective audit of management of GCSE in my current hospital over the last six months, with a focus on management of benzodiazepine-resistant cases & the American guideline as my relevant standard.

However, the limitations of this study cannot be discounted. It is important that the question of the best AED to use in benzodiazepine-resistant GCSE in patients on maintenance AEDs be answered, given that these patients comprise a significant proportion of those attending emergency departments with convulsive status. This should be addressed with subgroup analysis of patients enrolled in this study, followed by dedicated further investigation.

#### References:

1. Alvarez, V., Januel, J., Burnand, B. and Rossetti, A. (2011). Second-line status epilepticus treatment: Comparison of phenytoin, valproate, and levetiracetam. *Epilepsia*, 52(7), pp.1292-1296.
2. Yasiry, Z. and Shorvon, S. (2014). The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A metaanalysis of published studies. *Seizure*, 23(3), pp.167-174.
3. Glauser, T., Shinnar, S., Gloss, D., Alldredge, B., Arya, R., Bainbridge, J., Bare, M., Bleck, T., Dodson, W., Garrity, L., Jagoda, A., Lowenstein, D., Pellock, J., Riviello, J., Sloan, E. and Treiman, D. (2016). Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Currents*, 16(1), pp.48-61.
4. NICE Guideline 'Epilepsies: diagnosis and management Clinical guideline [CG137] Published date: January 2012 Last updated: October 2019'