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Psychiatric adverse events in patients with focal seizures receiving adjunctive eslicarbazepine acetate in a Phase IV clinical trial

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Purpose: The objective of this post-hoc analysis was to report psychiatric treatment-emergent adverse events (TEAEs) with eslicarbazepine acetate (ESL) in a real-world clinical setting.
Method: This was a multicenter, open-label, non-randomized Phase IV study of adjunctive ESL in patients aged ≥ 18 years with focal seizures in the US and Canada (NCT03116828). Arm 1: patients received ESL as first adjunctive therapy with levetiracetam (LEV) or lamotrigine (LTG); Arm 2: patients received ESL as a later adjunctive therapy, following current or prior use of adjunctive therapy. Data were collected on TEAEs, medical history of psychiatric disorders, and concomitant psychotropic medications. A Kaplan–Meier curve was performed for time to first psychiatric disorder TEAE, with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated.
Results: Psychiatric disorder TEAEs occurred in 14% of patients (6/44) in Arm 1 and 28% of patients (16/58) in Arm 2. In Arm 1, a psychiatric TEAE occurred in 83% (5/6) of patients with a history of psychiatric disorders versus 42% (16/38) without; and in 50% (3/6) of patients who were taking a psychotropic medication versus 24% (9/38) who were not. In Arm 2, a psychiatric TEAE occurred in 56% (9/16) of patients with a history of psychiatric disorders versus 38% (16/42) without; and in 38% (6/16) of patients who were taking a psychotropic medication versus 19% (8/42) who were not. Time to first psychiatric disorder TEAE showed that psychiatric TEAEs were more likely to appear earlier in Arm 2 than in Arm 1; however, the differences were not significant (HR: 2.295; 95% CI: 0.898–5.870; p=0.083).
Conclusion: Psychiatric disorder TEAEs were more frequent in patients with a history of psychiatric disorders or who were taking psychotropic medications and tended to be reported earlier in patients receiving adjunctive ESL as later versus first adjunctive therapy.

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Time to baseline seizure count in patients with focal seizures receiving adjunctive eslicarbazepine acetate in a Phase IV clinical trial

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Purpose: The objective of this post-hoc analysis was to determine the time required to reach baseline seizure count as an alternative way of assessing efficacy with eslicarbazepine acetate (ESL) in patients with relatively low monthly seizure frequencies at baseline in a real-world clinical setting.
Method: This was a multicenter, open-label, non-randomized Phase IV study of adjunctive ESL in patients aged ≥ 18 years with focal seizures in the US and Canada (NCT03116828). Arm 1: patients received ESL as first adjunctive therapy with levetiracetam (LEV) or lamotrigine (LTG); Arm 2: patients received ESL as a later adjunctive therapy, following current or prior use of adjunctive therapy. The endpoints analyzed were time to individual total baseline seizure count, time to ESL discontinuation, time to first treatment-emergent adverse event (TEAE), and time to first dizziness TEAE. Kaplan–Meier curves, hazard ratios (HRs) and 95% confidence intervals (CIs) were generated.
Results: The time to reach individual baseline seizure count showed that patients in Arm 1 reached their baseline seizure count later than patients in Arm 2 (HR: 2.131; 95% CI: 1.262–3.598; p=0.005). Patients in Arm 1 also had a longer time to ESL discontinuation than patients in Arm 2 (HR: 2.343; 95% CI: 1.037–5.293; p=0.041). There was no difference in time to baseline seizure count or time to ESL discontinuation in either arm according to concomitant LEV vs LTG. Time to first TEAE showed no significant difference between arms; however, in Arm 1, patients receiving concomitant LTG reported TEAEs earlier than those receiving LEV (HR: 2.379; 95% CI: 1.166–4.852; p=0.017). Time to first TEAE of dizziness did not differ between arms.
Conclusion: The time to reach individual baseline seizure count and time to ESL discontinuation was longer in patients with focal seizures receiving ESL as a first versus later adjunctive therapy.

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Effect of modal and maximum dose in patients with focal seizures receiving adjunctive eslicarbazepine acetate in a Phase IV clinical trial

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Purpose: The objective of this post-hoc analysis was to determine how various doses of eslicarbazepine acetate (ESL) impacted efficacy endpoints in a real-world clinical setting.
Method: This was a multicenter, open-label, non-randomized Phase IV study of adjunctive ESL in patients aged ≥ 18 years with focal seizures in the US and Canada (NCT03116828). Arm 1: patients received ESL as first adjunctive therapy with levetiracetam (LEV) or lamotrigine (LTG); Arm 2: patients received ESL as a later adjunctive therapy, following current or prior use of adjunctive therapy. The endpoints analyzed were percent change from baseline in standardized seizure frequency (SSF) and the proportions of patients completing the 24-week maintenance phase according to modal or maximum ESL dose.
Results: Dosing was at the discretion of the investigator based on patient needs and doses ranged between 800 and 1600 mg. Stratification of median SSF at baseline and median change from baseline in SSF by modal or maximum ESL dose showed that the previously reported 72.8% reduction in SSF in Arm 1 and 68.6% reduction in SSF in Arm 2 patients receiving LEV (Hixson J, et al. Epilepsy Res 2021;171:106561) was mostly attributable to receipt of the modal/maximum ESL dose of 800 mg and was also mostly responsible for the retention rates of 81.8% and 63.8% seen in Arm 1 and Arm 2, respectively. Of the patients in Arm 1 and Arm 2 receiving a modal dose of 800 mg, 30/33 (90.9%) and 27/40 (67.5%) completed the 24-week maintenance period.
Conclusion: Stratification of the data showed that retention rates and reduction in SSF at 24 weeks is mostly driven by patients receiving the lowest allowed ESL maintenance dose of 800 mg, regardless of whether ESL was taken as a first or later adjunctive therapy.

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Is anti-seizure drug the culprit of SUDEP?

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Purpose: HRV reduction is a potential biomarker for sudden cardiac death. Whether anti-seizure drugs (ASDs) are related to the reduction in HRV in epilepsy or related to SUDEP has been controversial. This study aimed to study the effects of ASDs, adjusted with reported factors associated with SUDEP on HRV parameters.
Method: We recruited all patients who were admitted in our epilepsy monitoring unit for 24-hour video-EEG monitoring, between January 2013 and December 2021. Two 5-minute ECG epochs were selected in each patient. HRV analysis with Python® software was performed. The imputed datasets were used for linear regression analysis to assess association between each ASD item and all HRV parameters. The effects of ASD on HRV parameters were subsequently adjusted with the significant clinical characteristics and the concomitant use of other ASDs respectively.
Results: Four ASDs including carbamazepine (CBZ), levetiracetam (LEV), lamotrigine (LTG) and clonazepam (CZP) were statistically significant associated with changes of sleep HRV parameters (BPM, SDNN, HF). Only CBZ showed negative effects with reduction in HRV, evidenced as lower SDNN, even when adjusted with concomitant use of other ASDs (β-coefficient = -11.385, p = 0.045) and had a trend of significance when adjusted with significant clinical characteristic of concurrent taking beta-blocker drug (β-coefficient = -10.663,p = 0.052). LEV and CZP showed opposite effects with increased HRV even when adjusted with significant clinical characteristics and the concomitant use of other ASDs.
Conclusion: CBZ showed negative effects on HRV. We proposed that CBZ should be cautiously used in patients with known risks for SUDEP i.e., advanced age, prolonged history of epilepsy, frequent GTCs and presence of nocturnal seizures. In addition, HRV assessment should be performed prior to commencing CBZ and re-performed in follow-up in case of prolonged use.

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Seizures related to non-ketotic hyperglycemia: 3 case reports

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Purpose: Seizures induced by non-ketotic hyperglycemia (NKH) are rarely encountered in daily clinical practice, they occur generally after the age of 50 years and are mostly focal and resistant to antiepileptic drugs (AEDs). We emphasis on the importance of an early hyperglycemia correction in seizures control.
Methods: 3 case reports of patients hospitalized in our department between November 2020 and July 2021.
Results: L.B 69 years old, diabetic for 20 years. He had a focal motor seizure involving the right hemibody with impaired awareness followed by confusion and right hemiparesis resolving slowly over 10 days, the initial blood glucose was above 33.4 mmol/L and the brain MRI, lumbar puncture (LP) and the complete metabolic workout were unremarkable. Mrs. G.H 55 years old, diabetic for 6 years. She had focal motor seizures starting from her left hemibody then becoming generalized, followed by aphasia and right hemiplegia resolving after 3 days. Initial blood glucose was 19 mmol/L. Mr. H.F 36 years old, diabetic since the age of seven. He presented epilepsia partialis continua (EPC) of his right hemibody for 20 days, seizures were resistant to antiepileptic drugs and were only controlled after blood glucose correction. The initial blood glucose was 30 mmol/L. The 3 patients had no history of epilepsy, they had NKH superior to 16.6 mmol/L, seizures were motor, followed by Todd's paresis and had focal onset with bilateralization in the first two cases which is typical in NKH, the 3rd patient presented with EPC which was also reported.
Conclusion: The new onset of seizures in diabetic patients must always lead to suspicion of NKH, AEDs are inefficacious and seizures are only controlled by glycaemia normalization and rehydration.

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The association of multiple chronic conditions and healthcare expenditures among adults with epilepsy in the United States: results from the Medical Expenditure Panel

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Purpose: Epilepsy is a multifaceted chronic neurologic disease that puts a serious strain on the financial standings of a large group of patients across the country. With healthcare costs so high at baseline for patients with epilepsy, it begs the question of whether the co-occurrence of multiple chronic conditions (MCC) can impose further financial strain on this patient population.
Methods: Using 12 years (2003-2014) of MEPS-HC (Medical Expenditure Panel Survey Household Component) data, a retrospective study was conducted to evaluate the relationship between chronic conditions and epilepsy-related healthcare expenditures sampling from 1,942,413 patients with epilepsy. Patients were categorized as having 0, 1, or 2 chronic conditions in addition to epilepsy.
Results: Over half of the patients with epilepsy had at least two chronic conditions (CC). The results showed a statistically significant increase in likelihood of having at least 2 CCs in female patients, unemployed patients, and those who were never married. Patients with epilepsy who had at least 2 CCs were also found to perceive their health as very good at a much lower rate than those with no CCs. Importantly, patients with no CC had less total healthcare costs (mean: $6,177; CI: $4,895-$7,459) when compared to patients who do have multiple CCs (mean: $21,277; CI: $12,971-$25,583). Within various cost categories, expenditures increased with the number of CC found in these patients.
Conclusion: As this is the first known study to investigate the association between epilepsy and the presence of MCC, the results provide new insight as to how MCCs can impact healthcare costs for patients with epilepsy. The data could prove resourceful in establishing improved guidelines for epileptic care, possibly leading to an overall reduction in healthcare expenditures. A potential intervention to improve outcomes could involve bettering specialized epilepsy care that focuses on the treatment of patients' MCCs.

Basic science

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Genetic susceptibility to acquired epilepsy affects seizure progression after amygdala kindling: validation of the FAST and SLOW rat models

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Purpose: Animal models are valuable tools to study how genetic predisposition influences acquired epileptogenesis. Previously, Racine and colleagues (1999) have developed selectively-bred rat strains with different susceptibility to evoked seizures using the amygdala kindling model, designated as FAST (seizure-prone) or SLOW (seizure-resistant). This study aimed to validate the phenotypes of our current FAST & SLOW rat colony to experimental amygdala kindling and to evaluate the seizure susceptibility of their F2 generation progeny.
Method: A stimulating bipolar electrode was inserted into the left amygdala of 11-week-old male rats—FAST (n= 10), SLOW (n= 14) and their F2 generation (n= 68). One week post-surgery, the after-discharge threshold to generate an electrographic seizure of >5 sec was determined. Rats then either received a maximum of 30 kindling stimulations (2/day, 5 days/week) or until 5 class V seizures were observed (i.e., fully kindled).
Results: FAST rats required fewer stimulations to fully kindle compared to SLOW rats ($p < 0.001$), with all animals fully kindled within 30 stimulations. The F2 generation required fewer stimulations to fully kindle compared to SLOW rats ($p < 0.01$) but were comparable to FAST rats. Total seizure duration was also significantly shorter for SLOW rats compared to FAST and F2 rats for the first 12-15 stimulations.
Conclusion: Differences in kindling profiles between FAST, SLOW rats and their F2 generation suggest that differences in susceptibility to acquired epileptogenesis are genetically inherited. This finding supports further investigation of candidate genes and proteins in this model which may explain inherent susceptibility to acquired epilepsy in humans.
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Highlighting molecular and electrophysiological impairment of neurons derived from a patient affected by febrile seizures and mesial temporal lobe epilepsy using induced pluripotent stem cells technology

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Purpose: Retrospective studies have linked childhood febrile seizures (FS) to the development of mesial temporal lobe epilepsy (MTLE) later in life. To investigate mechanisms that could be at the basis of the two pathologies, we generated a cellular model using pluripotent stem cell-derived neurons (idNs) from a patient affected by both FS and MTLE and carrying the c.434T>C mutation in *SCN1A* gene, codifying for the voltage gated sodium channel (VSVG) $Na_V1.1$.
Method: the patient belongs to a family in which fourteen members carry the mutation mentioned above (Mantegazza M et al. PNAS 2005;102:18177–18182). The mutation leads to the substitution of a highly conserved methionine residue with a threonine in the position 145 of the protein (M145T). Our patient is the only one experienced a putative example of complex FS and, with two other component of the family, developed afebrile seizures in the temporal lobe a few years later after FS offset (Colosimo E. Epilepsia 2007; 48:1691–1696). We compared the idNs obtained from the patient with those of a healthy control using a combination of molecular and electrophysiological analysis.
Results: our neuronal differentiation protocol gave a prevalence of gabaergic neurons in the culture (about 90% of $GAD1^+$). We found a lower expression of *SCN1A* and *SCN2A*in idNs carrying the mutation in respect to those of the control during time in culture, while an opposite trend is observed for *SCN3A*, known to be a more fetal-like isoform. Moreover, we found a high *NKCC1*/*KCC2* ratio (both genes codifying for chloride co-trasporters) in $SCN1A^{M145T}$-idNs, indicative of neuronal immaturity. Patch-clamp measurements revealed depolarized action potential for $SCN1A^{M145T}$-idNs suggesting a reduced excitability.
Conclusion: Altogether, our results highlighted that a delayed development of neurons with the $SCN1A^{M145T}$mutation can contribute to the FS and MTLE pathologies.

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Characteristics of epilepsy in 73 girls with Rett syndrome: a thirty-year experience of a tertiary centre in Serbia

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Purpose: Determining the characteristics of epilepsy in patients with Rett syndrome.
Method: A retrospective study included all patients treated in inpatients and/or outpatients clinic at the Mother and Child Healthcare Institute between 1986 to 2016 and meeting clinical criteria for diagnosing Rett syndrome. Female patients with epilepsy were subject to special analysis: the monitoring covered the age when the first seizure had occurred, the semiology of seizures, the presence of one or more types of seizures. It was observed whether the frequency of seizures was monthly, weekly, or daily. The efficacy of the first antiepileptic drug was determined, as well as whether epilepsy was well-controlled or drug-resistant.
Results: The study included 94 girls diagnosed with Rett syndrome. The average age of the girls at the time of analysis was 177.46 months. Epilepsy occurred in 73 (77.7%) girls. A good seizure control was achieved in 46.2% and drug-resistance was developed in 53.8% of the patients. Regression in development usually occurred between months 19 and 36. Microcephaly was present in 94.8% and stereotypes in 97.6% of the patients. The average age when the first epileptic seizure occurred was 41.58 months. The most common types of seizures were generalized tonic-clonic seizures (35 patients) and seizures with focal onset and with impaired awareness (33 girls). A single type of seizure occurred in 45.6% of the patients, whereas 54.4% had multiple types of seizures; 5 patients had a status epilepticus. For 19 patients the outcome was fatal.
Conclusion: The occurrence of drug-resistant epilepsy in patients with Rett syndrome depends on the age of regression onset, the presence of involuntary movements, the presence of tonic, aware focal onset seizures and epileptic seizures with focal onset and with impaired awareness, the existence of multiple types of epileptic seizures, and a higher frequency of epileptic seizures.

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How space changes astronauts' brains? The negative effects of space exposure on the central nervous system

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Purpose: To provide information about the prospects of aerospace research, it is noted that brain changes predispose to a risk of convulsion in long-term astronauts and persistent headaches more than 72 hours after travel. Previous studies and observations of astronauts and cosmonauts returning from long missions aboard space stations have shown significant unforeseen concerns. Countermeasures to protect astronauts from space exposure require further exploration and are vital components to ensure a safe and reliable trip to Mars.
Method: standardized bibliographic review, with the comparison of case reports through NASA-USA support. a review of 100 research articles was developed, producing a complete analytical report of the evidence up to the time of aerospace medicine and its neurological effects.
Results: The main findings are tension headache during and after astronaut travel, there are also imaging findings of participants in space travel and without space travel exposed to microgravity models with demyelination, axonal loss or edema, as a side effect on brains exposed to microgravity.
Conclusion: Maintaining neurological function in long-term travel through space exposure is vital for both astronaut health and mission safety. There is a risk of long-term neurological sequelae, predisposing to headaches, convulsions and cognitive impairment.

Bridging the treatment gap

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Drive or not drive: 3A-2F-VM app for determination of seizure risk

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Introduction: Legislated restrictions to drive in people with epilepsy may not be applied to the patients with first unprovoked seizure (FS) since rate of recurrence is less. Individual risk assessment for FS is required.
Objectives: To develop a clinical prediction model for seizure recurrence in patients with FS.
Materials and Methods: We recruited all FS patients who had CT or MRI performed from our adult EEG database. Previously reported significant factors along with detailed EEG/imaging findings, comorbidities and comedications were included as potential risk factors. We considered a first seizure recurrence as our study outcome. Cox proportional hazard model was used. Assigning point to the significant factors was then performed based on their β-coefficients. Risk level according to sum points was classified as low, medium and high. Associated risk of seizure recurrence, annual incidence rate and median time to seizure recurrence were reported.
Results: 116 FS patients were recruited. Multivariate analysis revealed 7 independent risk factors including ADHD (HR 5.39), on Antidepressants at the time of FS (HR 0.16), Antiseizure medications started after FS (HR 0.43), Family history of epilepsy (HR 5.17), Focal aware seizure as a seizure type of FS (HR 3.60), Valvular heart disease as a comorbidity (HR 6.67) and presence of Microbleeds on MRI (HR 3.31). These factors were assigned + 2, - 2, - 1, + 2, + 1, + 2 and + 1 points, respectively. Individual sum points were classified as low (-3 to -1), medium (0) and high (+ 1 to + 8). High-risk FS patients carries highest recurrence rate of 89.47%, with median time to first seizure recurrence of 4.32 months.
Conclusion: Our study provides "3A-2F-VM App score" individually assessing the patient's risk. Based on our model, the high-risk FS patients should be compulsory avoided from driving for at least 12 months.

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Health disparities in pediatric epilepsy: the impact of language-concordant care

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Purpose: Health disparities/inequities disproportionately affect racial/ethnic minorities, people with low socioeconomic status (SES), the underinsured and people with limited English proficiency (LEP). The goals of this study are to document the extent of disparities among Hispanic pediatric epilepsy patients, and explore the contributions of LEP, health literacy, SES and insurance status to these outcomes. We hypothesize 1) Hispanic ethnicity and LEP will be additive risk factors for poor outcomes, and 2) language concordance between caregivers and providers will diminish the health disparities of LEP patients.
Methods: A prospective observational study is being conducted comparing 4 pediatric epilepsy populations over 5 years:

1. Spanish-speaking LEP patients/caregivers seen by language concordant (Spanish-fluent) providers
2. Spanish-speaking LEP patients/caregivers seen by language-discordant providers with interpreters
3. English-proficient Hispanic patients/caregivers,
4. English-proficient white, non-Hispanic patients/caregivers.

Patients meeting inclusion/exclusion criteria are recruited prior to their new patient appointment. Demographic data are obtained and questionnaires are administered at intake and every 6 months. Provider documentation and orders are obtained from the EHR at similar time points.
Results: More than 40 families have been enrolled. Preliminary data suggest:

1. LEP patients are more likely to be referred by pediatricians than by hospitals/EDs.
2. Hispanic patients, regardless of English proficiency, experience longer delays between referral and new patient appointment.
3. LEP and Hispanic ethnicity are additive risk factors for lower epilepsy knowledge.
4. Language discordant providers are less likely to document discussion of common epilepsy comorbidities.
5. Language discordant providers tend not to refer LEP patients for specialty evaluation (e.g. psychology, neuropsychology).

Conclusions: Preliminary data suggest Hispanic patients with and without LEP arrive at their new patient appointments already at a disadvantage. LEP patients seen by language discordant providers appear to receive a lower quality of care. Several theories on the underlying mechanisms of these disparities are explored.

Clinical Neurophysiology

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Benefits of routine inpatient eeg in practice: experience from a level 4 university hospital

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Purpose: Routine inpatient EEGs are commonly studied and ordered. We aim to improve current routine EEG practices by studying their role at a large university hospital. This study aims to analyze these practices and the effect it has on treatment outcomes and management.
Methods: Inpatient routine EEGs from January -July 2021 were included and patients <5 yrs., repeat EEGs were excluded. Charts were reviewed for indications, floor status, abnormality, day of study, neurology consultation, results, treatment changes, discharge status and prior AED use. Statistical analyses using SAS 9.4 were performed.
Results: From 285 patients, 250 included were of mean age 57.27 yrs., where 54.22% were males and 45.78% females. Indications listed were 26.5% altered mental status, 59.83% seizures and 13.65% others. 87.36% ICU patients had abnormal EEG vs 73.75% floor patients. Significant association was found between floor status and EEG results. Abnormalities were 44% generalized slowing, 23.6% focal slowing, 9.2% epileptiform activity and 23.2% others. Treatment was changed in 21.03% with abnormal vs 5.56% with normal EEG. AEDs were added in 18.46% with abnormal vs 3.7% with normal EEG. Significant association was found between Neurology consultation and treatment change and with AED addition respectively. EEG result was associated with treatment change and AED addition.
“Abnormal EEG” was significantly associated with a further study. cEEG/MRI Brain/LP was done in 22.05% with abnormal vs 9.26% with normal EEG. Significant association was found between EEG results and discharge status, but not between weekday and discharge status nor between EEG results and duration of study. 53.82% patients were not on AED before EEG vs 46.18%. Prior AED had no association with EEG results.
Conclusions: It is helpful to consult Neurology. Longer duration of routine EEGs does not show abnormalities/seizures. Prior AED use does not affect outcomes. Routine EEG facilitates discharges and guides further management.

Comorbidities

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Pilot to evaluate VR-therapy on people with epilepsy and related anxiety disorders

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Purpose: Exposure therapy (ET) is helpful in managing anxiety in People with Epilepsy (PwE) (Blocher et al. Epilepsy & Behavior 2013;27:70-76; Newsom-Davis et al. Seizure 1998;7:101-106). Virtual Reality (VR) has shown to be an effective tool for delivering ET for a number of anxiety disorders (Deng et al. Journal of Affective Disorders 2019;257:698-709). The use of an immersive-VR (using mobile-headsets) to deliver ET in this population offers several benefits, but to our knowledge no research has been conducted to-date on VR-ET in PwE.
We are designing and rigorously evaluating a VR-ET program administered in private residences that focuses on decreasing anxiety in PwE.
Methods/Results: Our pilot study consists of three phases: 1) Engagement with those with lived-experience (target n=15) via online surveys to identify and validate 3 scenarios with 3 levels each that create anxiety in PwE. Participants will either have epilepsy themselves or be affected by it (for example, through a family member with epilepsy). 2) Film nine 360-degree VR-videos (3 scenarios x 3 levels each based on data consolidated from Phase 1 and literature reviews) for the minimal viable product. 3) We will run a pilot clinical trial that will be listed on clinicaltrials.gov. Specifically, this prospective experimental study will evaluate the impact of the VR-ET on PwE (target n=10) using mixed-methods. We will measure changes in self-reported anxiety (GAD-7; HADS-A; brEASI; diagnostic protocol by Hingray et al. 2019 pages 5-7) over two-weeks as participants transition through the levels within each scenario. We hypothesize that levels of epilepsy/seizure-related anxiety will decrease from using VR-ET. Preliminary results will be available by April 2022.
Conclusion: This study will contribute to the limited body of research that currently exists on managing anxiety in PwE. Findings from our pilot will inform the methods for our subsequent larger clinical trial.
Acknowledgement: York University

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Results of first-in-human, Phase 1 clinical trials of ETX-155 - a novel clinical stage neuroactive steroid $GABA_AR$ (gamma-aminobutyric acid A receptor) positive allosteric modulator

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Purpose: ETX-155, is a potent and selective positive allosteric modulator (PAM), targeting synaptic and extra-synaptic $GABA_AR$. ETX-155 has shown antiepileptic activity and antidepressant/antianxiety properties in preclinical models, indicating its potential to be a mood-elevating antiseizure medication (ASM). Here we report two phase 1 studies: one single-ascending/multiple-dose study and one multiple-dose study. These were single-center, double-blind, randomized placebo-controlled studies to determine safety, tolerability, and pharmacokinetics (with/without food) of ETX-155.
Method: In the single-ascending dose (SAD) study, single morning doses of 5, 15, 30 (fasted/fed), 60, 90, or 135mg ETX-155 (6/cohort) or placebo (2/cohort) were administered after a 10h fast. A 7th cohort (200mg) was stopped after 1 of 2 sentinel subjects met a prespecified stopping rule. Blood samples for pharmacokinetics were collected up to 48h after dosing. In the multiple-dose studies (MAD), a total of 3 cohorts received 60mg ETX-155 or placebo once-daily, morning or evening for 7-days, or evening for 14-days.
Results: A dose-proportional increase in area under the concentration curve (AUC) and maximum plasma concentration (Cmax) was observed across the single-dose range of 5-200mg, with small/moderate inter-subject variability (coefficient of variation ≤33%). After a single-dose, time of maximum concentration was 2-4h; half-life was 21-27h. In the 14-day multiple-dose study, steady-state was reached at day 8, with a terminal half-life of ~40h. Across studies, mild/moderate dizziness and somnolence were the most common (11-60%) adverse events (AEs), reported primarily after morning administration. The maximum tolerated single dose was 135mg. No clinically meaningful food effect was observed. No serious AEs, discontinuations, or significant abnormalities in vital signs, electrocardiograms, or laboratory parameters occurred with the 5-135mg single dose range or the 60mg repeat dose of ETX-155.
Conclusions: ETX-155 is a well-tolerated $GABA_AR$ PAM with the potential to be an ASM with antidepressant and antianxiety effects.

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Perampanel as early add-on therapy for epilepsy patients with focal-onset and generalised-onset seizures treated in clinical practice

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Purpose: To assess the real-world effectiveness and safety/tolerability of perampanel (PER) when used as early add-on therapy in everyday clinical practice.
Method: Patients treated with PER for focal-onset and/or generalised-onset seizures were identified from a pooled analysis of 44 prospective/retrospective/cross-sectional clinical practice studies. Data were compared for patients treated with PER as early versus late add-on therapy (as defined by each study). Retention was assessed after 3, 6 and 12 months of PER treatment. Effectiveness assessments comprised responder rate (≥50% seizure frequency reduction), seizure freedom rate (no seizures since at least the prior visit), and proportions of patients with unchanged or worsening seizure frequency. Adverse events (AEs), psychiatric AEs, and AEs leading to discontinuation were evaluated.
Results: 2532 patients were treated with PER as early (n=632) or late (n=1900) add-on therapy; median number of concomitant antiepileptic drugs were 1 and 3 at baseline, respectively. Retention rates were significantly higher for patients treated with early versus late add-on therapy at all timepoints (Month 12: 77.1% vs. 61.8%; p<0.001). At last visit, seizure freedom rate was significantly higher in patients treated with early versus late add-on therapy (40.1% vs. 8.7%; p<0.001), as was responder rate (73.0% vs. 36.4%; p<0.001); and the proportion of patients with unchanged seizure frequency was significantly lower in the early versus late add-on group (10.2% vs. 31.8%; p<0.001), as was the proportion of patients with worsening seizure frequency (6.1% vs. 13.6%; p<0.001). Patients treated with early versus late add-on therapy had a significantly lower incidence of AEs (41.8% vs. 54.5%; p<0.001), psychiatric AEs (18.3% vs. 22.2%; p=0.046), and discontinuation rates due to AEs at 12 months (15.0% vs. 18.7%; p=0.045).
Conclusion: PER was significantly more effective and better tolerated when used as early versus late add-on therapy to treat patients in everyday clinical practice.
Supported by Eisai

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Efficacy and safety of adjunctive perampanel for myoclonic and absence seizures: post hoc pooled analysis of adult, adolescent, and pediatric patients in studies 332, 311, and 232

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Purpose: Here, we performed a post hoc pooled analysis of Phase III and Phase II studies to assess the efficacy and safety of adjunctive perampanel for myoclonic and absence seizures in adult, adolescent, and pediatric patients.
Method: In Study 332 (NCT01393743), adolescent/adult patients aged ≥12 years with idiopathic generalized epilepsy and generalized tonic-clonic seizures (GTCS) received placebo or adjunctive perampanel 8 mg/day. In Study 311 (NCT02849626), pediatric patients aged 4 to <12 years with focal-onset seizures or GTCS received open-label perampanel up to 16 mg/day. In Study 232 (NCT01527006), pediatric patients aged 2 to <12 years with epilepsy received open-label perampanel up to 0.18 mg/kg/day. For these analyses, data from patients with myoclonic and/or absence seizures during baseline were pooled. Assessments included median percent change in seizure frequency/28 days, 90% responder rates, and treatment-emergent adverse events (TEAEs).
Results: Of 393 patients, 66 had myoclonic seizures (placebo, n=23; perampanel, n=43) and 72 had absence seizures (placebo, n=33; perampanel, n=39) at baseline; patients with both seizure types are counted in both groups. Median percent reductions in seizure frequency/28 days were observed in the placebo and perampanel groups: myoclonic, 52.5% and 24.6%; absence, 7.6% and 25.1%, respectively. For placebo and perampanel, 90% responder rates were: myoclonic, 26.1% (n=6/23) and 14.0% (n=6/43); absence, 18.2% (n=6/33) and 25.6% (n=10/39), respectively. TEAEs with placebo and perampanel occurred in 18 (78.3%) and 36 (83.7%) patients with myoclonic seizures, and 25 (75.8%) and 34 (87.2%) patients with absence seizures, respectively. With perampanel, the most common TEAEs were dizziness and fatigue.
Conclusion: Despite small patient numbers, these data suggest adjunctive perampanel does not worsen myoclonic or absence seizures in adult, adolescent, and pediatric patients. Seizure reductions were observed for both seizure types; however, this analysis was not powered to make comparisons between placebo vs perampanel.
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Real-world healthcare costs related to long or short-half-life antiseizure medication use

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Purpose: Long half-life (LHL) antiseizure medications (ASMs) remain in systemic circulation longer compared with short half-life (SHL) ASMs. A LHL-ASM (>20 hours) may be more protective of missed doses, at any adherence level, resulting in better efficacy and improved outcomes. Our objective was to compare healthcare costs in patients treated SHL- versus LHL-ASMs.
Methods: This retrospective cohort study used the IBM MarketScan® Research database to identify patients ≥18 years old with epilepsy (≥2 medical claims ≥30 days apart),≥2 fills for an SHL or LHL-ASM (first fill was index date) between 1/1/2016–12/31/2018, and 12 months' continuous enrollment pre- and post-index. Patients who received any ASM in the pre-index period or both SHL plus LHL-ASM post-index were excluded. Adherence was assessed over the 12-month post-index period using the proportion of days covered (PDC). Medical claims were used to estimate healthcare costs, where epilepsy-related costs were defined as a claim that had a primary or secondary epilepsy diagnosis code. A generalized linear model with gamma distribution was performed for adjusted healthcare costs.
Results:A total of 7,144 patients were identified (4,866 SHL, 2,278 LHL). Compared to SHL, patients receiving LHL-ASMs were significantly younger (37.7 versus 43.4 years, p<0.001) and less comorbid [Charlson comorbidity index: 0.6 versus 1.7, p<0.001]. Adherence to therapy was similar between SHL and LHL-ASM (mean PDC 0.65 vs. 0.63). Patients receiving LHL-ASMs had lower mean all-cause per-patient-per-month (PPPM) costs ($1,365 vs. $4,282) and epilepsy-related ($273 vs. $610) (all p<0.001). After adjusting for demographics and clinical characteristics, LHL-ASM users had lower PPPM mean all-cause costs ($2,028 vs. $3,942) and lower epilepsy-related costs ($293 vs. $553) (all p<0.001).
Conclusion: Patients treated with LHL monotherapy had a lower economic burden compared with those treated with SHL, indicating that using ASMs with a longer half-life is associated with lower healthcare costs.

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Safety and time to second doses in pediatric and adult patients with seizure clusters treated with diazepam nasal spray in a Phase 3, open-label, repeat-dose safety study

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Purpose: Diazepam nasal spray is approved for acute treatment of seizure clusters (SC) in patients with epilepsy aged ≥6 years. Safety and time to second dose (proxy for effectiveness) in patients aged 6-11 years and ≥12 years was assessed from the long-term, phase 3, open-label, repeat-dose safety study of diazepam nasal spray.
Method: Patients aged 6-65 years received 5-20 mg doses of diazepam nasal spray based on age (≤11, ≥12 years) and weight. Second doses could be administered 4-12 hours later if needed. Investigators could adjust doses for effectiveness/safety. Seizures, drug administration, second doses, and treatment-emergent adverse events (TEAEs) were recorded.
Results: Among 163 treated patients (6-11 years: 27.6%, ≥12 years: 72.4%), exposure was ≥12 months in 35/45 (77.8%) of the 6-11 group and 98/118 (83.1%) of the ≥12 group. The 6-11 group experienced 784 SC and used 90 (11.5%) second doses (22 in <4 hours, 7 in 4-6 hours, 22 in 6-12 hours, 39 in 12-24 hours). The ≥12 group had 3069 SC and used 395 (12.9%) second doses (130 in <4 hours, 65 in 4-6 hours, 234 in 6-12 hours, and 105 in 12-24 hours). TEAEs occurred in 91.1% of patients in the 6-11 group; 40.0% were serious, and 6.7% considered treatment-related. In the ≥12 group, 78.8% experienced TEAEs; 27.1% were serious (including 1 death, not treatment related), and 22.9% considered treatment-related. No serious TEAEs were considered treatment related. Retention rates until study closure were 75.5% and 76.3% for the 6-11 and ≥12 groups, respectively.
Conclusions: In a long-term safety study of diazepam nasal spray, use of second doses, safety, and retention rate was similar across age subgroups. Second doses were administered within 24 hours for 11.5% and 12.9% of SC among patients 6-11 and ≥12 years, respectively. Safety profile was consistent with rectal diazepam.

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Long-term efficacy and safety of perampanel monotherapy in patients with newly diagnosed/currently untreated recurrent focal-onset seizures: FREEDOM study 342 extension phase

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Purpose: FREEDOM (NCT03201900) showed that perampanel 4–8 mg/day monotherapy was efficacious and generally well tolerated in patients aged ≥12 years from Japan/Korea with newly diagnosed/currently untreated recurrent focal-onset seizures (FOS), with/without focal to bilateral tonic-clonic seizures. We report long-term (52 weeks; up to a maximum of 24 months) efficacy and safety from the Extension Phase.
Method: During the Core Study, patients received perampanel 4 mg/day (4-week Pretreatment [baseline]; 32-week Treatment [6-week Titration; 26-week Maintenance] with the possibility to up-titrate to 8 mg/day). Patients could enter an Extension Phase for an additional 26 weeks (52 weeks). 52-week and 24-month seizure-freedom rates and treatmentemergent adverse events (TEAEs) (Core/Extension) were assessed.
Results: Overall, 89 patients received ≥1 perampanel dose (Safety Analysis Set). Of these, 73 patients entered the 4-mg/day Maintenance Period (modified Intent-to-Treat Analysis Set); 21 patients entered the 8-mg/day Treatment Phase. Overall, 46/67 (68.7%) eligible patients entered the Extension (39 who completed the 4- or 8-mg/day Treatment Phase [4 mg/day, n=32; 8 mg/day, n=7] and seven who discontinued the 8-mg/day Treatment Phase); 38 patients completed the Extension and eight discontinued, most commonly due to withdrawal of consent (n=3 [6.5%]). Overall, 24/32 (75.0%) and 20/32 (62.5%) patients who entered the Extension from the 4-mg/day Treatment Phase while seizure free had sustained seizure freedom for 52 weeks and 24 months, respectively; corresponding values from those who entered from the 4 and/or 8-mg/day Treatment Phase were 31/39 (79.5%) and 22/39 (56.4%), respectively. TEAEs occurred in 74/89 (83.1%) patients, most commonly dizziness (38.2%).
Conclusion: Final results of FREEDOM suggest seizure freedom can be sustained during long-term (up to 24 months) treatment with perampanel monotherapy at doses as low as 4mg/day in patients with newly diagnosed/currently untreated recurrent FOS. Perampanel was generally well tolerated and no new TEAEs were reported.
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Examining change in the inter–seizure-cluster interval across time from a Phase 3, long-term open-label, repeat-dose safety study of diazepam nasal spray for the treatment of seizure clusters

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Purpose: Inter-seizure cluster intervals (ISCI) have been studied with use of prophylactic antiseizure medications; however, there are few data on effects of intermittent treatment of clusters on ISCI. Diazepam nasal spray is approved for acute treatment of seizure clusters in patients with epilepsy aged ≥6 years. This analysis explores ISCI in patients with epilepsy and seizure clusters from a long-term safety study of diazepam nasal spray to assess whether timing of seizure clusters changes with treatment over time.
Method: Patients (6–65 years) and caregivers administered age- and weight-based diazepam nasal spray doses in this 12-month safety study. ISCI was evaluated using 90-day periods for patients treated with ≥2 doses across Period 1 and the following 3 periods. Patients with consistent data in each of the first 4 periods also were analyzed. Paired*t* test assessed statistical significance.
Results: Of 175 patients enrolled, 163 received ≥1 dose of diazepam nasal spray (mean age, 23.1 years). Of 151 patients with ISCI data, 120 had data in Period 1 and another period; 76 had ≥1 ISCI in Periods 1–4 (ie, across 360 days). Mean change was significant in the 120-patient cohort (P<0.001); ISCI increased from 14.8 days in Period 1 (0–90 days; n=120) to 35.8 days in Period 4 (271–360 days; n=87). Mean ISCIs for the 76-patient cohort increased significantly (P<0.01), from 12.2 days (Period 1) to 25.7 days (Period 4).
Conclusion: Over 12 months, a statistically significant increase in ISCI was demonstrated in patients using diazepam nasal spray for clusters. The increase in time between clusters may reflect a salutary effect of cluster treatment. This raises the possibility that intermittent treatment alters the underlying biology of clusters, which should be evaluated with further studies.

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Canadian use of marijuana post-legalization among patients with epilepsy

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Purpose: Marijuana has long been used as an alternative treatment for epilepsy and the adverse effects of anti-seizure medications. Marijuana has become increasingly mainstream since Canadian legalization in 2018. However, data is lacking on marijuana's benefits and prevalence, while usage among epilepsy patients is growing. This study aims to evaluate marijuana usage in patients with epilepsy.
Methods: We conducted a Canadian cross-sectional survey investigating usage and perceptions of marijuana in patients suffering from epilepsy.
Results:264 surveys were completed by patients (n=219;83.3%) or their caregivers (n=44;16.7%). The mean respondent's age was 32.4(IQR=24-39) and 74.2%(n=193) were female. 23.4(n=61) are on disability and 48.5%(n=126) have been experiencing spells for >10 years. Spell frequency <1 per month (n=104;40.2%) and generalized epilepsy (n=139;55.4%) were most common. 76.0%(n=200) of participants have used marijuana and 44.5%(n=73) use marijuana for their epilepsy. However, 55.2%(n=90) started using marijuana before their epilepsy was diagnosed. 40.4%(n=65) use marijuana multiple times per day. Most consume cannabis products in the evening (n=108;69.7%), amount used has a median of 5g per week (IQR=0.5-10) and smoking is the most used method of consumption (33.5%, n=54). 65.4%(n=100) of users feel more comfortable using marijuana compared to other pharmaceuticals because it is "natural", but 40.6%(n=63) had some type of side effect, including impaired thinking. 80.3%(n=126) of users and 70.5%(n=43) of non-users believe that there is stigma towards marijuana users. Among all respondents, 71.6%(n=156) report stigma lessening since legalization. 78.8%(n=126) of marijuana users have discussed their usage with their doctor. In addition, 53.8%(n=84) reported no change in their marijuana usage after legalization.
Conclusion: Marijuana use among epilepsy patients is a controversial subject, increasingly discussed in Canada since legalization. Our study shows a high prevalence of epilepsy patients using marijuana. Healthcare providers should provide appropriate counselling on the benefits and limitations.

Epilepsy and Reproductive Health

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Bone metabolic disorders in young men suffering from epilepsy

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The **purpose** of the research is to study the markers of bone tissue metabolism, to identify metabolic and hormonal disorders in men with epilepsy aged 18-44 years.
Method: This study involved 40 young men. The exclusion criteria were the presence of diseases of the gastrointestinal tract and kidneys, current neurological pathology. Clinical-anamnestic, neurological, and biochemical methods were used (determination of calcium, phosphorus, and parathyroid hormone in blood serum). Normal parameters were considered to be included in the following intervals: for calcium, 2.02-2.6 mmol/l, for phosphorus, 1.3-2.26 mmol/l, for parathyroid hormone, 21-45 pg/ml.
Results: When studying the content of calcium in the blood serum, it was found that its average value was 2.230±0.039 mmol/L, it was within the normal range. However, in 4 men (10%) there was a decrease in it, in 1(2.5%) — an increase. The average serum phosphorus content was 1.370±0.071 mmol/L, which is the lower limit of the norm. In the individual study of phosphorus parameters, more pronounced changes were observed: a decrease in its content was detected in 18 (45%), an increase — in 5 (12.5%). The average parathyroid hormone content was 36.060±4.766 pg/ml. However, it was for parathyroid hormone that the most pronounced changes were detected within the group: in 15 men (37.5%), this indicator was increased, and in 7 (17.5%) sharply, in 12 (30%) it was reduced, and in 5 (12.5%) sharply reduced.
Conclusion: The study revealed violations of calcium-phosphorus metabolism and its regulating parathyroid hormone in young men with epilepsy. The analysis of the content's indicators of calcium in the blood serum shows that in almost all the subjects they were within the normal range, while in relation to other indicators, a pronounced imbalance was revealed. This is consistent with the literature data, but a thorough study is needed in the future.

Epilepsy in Older People

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Case series: surgery outcomes of refractory epilepsy in the elderly

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Purpose: Quantify changes in disease burden after surgical interventions in an elderly population afflicted with refractory epilepsy
Methods: We reviewed the charts of 17 patients over the age of 50 who underwent or were evaluated for surgical treatment of pharmacotherapy resistant epilepsy. 2 patients were excluded: one with an underlying diagnosis of brain tumor and the other due to limited data. We quantified seizure freedom using the International League Against Epilepsy (ILAE) classification system and recorded changes in pharmacotherapy post-intervention. We noted pre-surgical comorbidities and the development of surgical complications.
Results: 6 patients underwent stereo EEG and 2 underwent subdural grid intracranial evaluation. 10 patients underwent resection, 2 had a device implanted, and 2 had both a resection and device implantation. At follow up, 50% (n=7) of surgical patients received an ILAE classification of 1, achieving seizure freedom. The rest of the patients received an ILAE classification over 3, having one or more seizure days per year. 8 patients saw a reduction in polypharmacy after surgical intervention. All patients suffered from past medical issues involving neurological and cardiovascular disease. 2 patients had post-surgical complications due to exacerbations of underlying medical conditions.
Conclusion: Intracranial evaluation and surgical intervention with resection and/or device placement is a safe and effective method of treatment in the elderly population. Extra precautions should be taken after surgery in elderly patients with multiple medical comorbidities. Future research should explore the relationship between pre-existing health conditions and surgical outcomes in epilepsy patients.

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A tale of two infantile epilepsy syndromes in a low-resource setting (and how genetics helped us)

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Purpose: In Trinidad & Tobago, resources are limited, including genetic testing. We aim to describe two patients diagnosed via targeted genetics and outline the benefits of securing these diagnoses
Method:
1: A male neonate presented on day 5 of life with clusters of focal tonic seizures associated with apnea requiring rescue antiseizure drugs. He was not encephalopathic. No family history of epilepsy nor antenatal/delivery concerns. He was discharged within one week on phenytoin maintenance. He is currently 10-months-old and is steadily weaning off phenytoin, with appropriate developmental milestones.
2: A female neonate presented at 3-months of age with focal motor seizures (face and limbs) and atypical absence/eye blinking + congenital microcephaly + developmental delay. No family history of epilepsy nor antenatal/delivery concerns. She is currently 10-months-old, on levetiracetam, phenytoin and clonazepam and has global developmental delay.
Results: EEG
1: Normal until an ictal event was recorded - beginning with excessive and fast, narrow spike waves on the right side followed by spike and slow activity, with brief spread to the left side becoming bilateral synchronous. Subsequently, there was background attenuation on the right side followed by spike and slow waves
2: A symmetric background, but faster frequency than for patient's age. There was almost continuous left hemisphere, maximum central fast frequency with admixed sharp waves consistent with an area of epileptogenesis
Epilepsy gene Panel (pathogenic variants)
1: KCNQ2 deletion (entire coding sequence) – AD Benign Familial Neonatal Seizures
2: GABRB3 c.860C>T (p.Thr287Ile) – AD Early Infantile Epileptic Encephalopathy
Conclusion: In the era of genetics, we are trying to catch up. With targeted genome sequencing at a reasonable cost (approximately $370 USD total), medical healthcare professionals are able to diagnose and counsel patients on prognosis. Early intervention therapies and consideration for early epilepsy surgery can also be emphasized for intractable cases.

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COVID 19 and epilepsy care in resource poor countries: An IEEC collaboration

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Purpose: This study aimed to explore changes in epilepsy care delivery patterns and teleconsultation methods in resource-poor settings during and since the lockdown.
Methods: A cross-sectional online survey was conducted among healthcare professionals (HCPs) (N=240) from 23 countries caring for people with epilepsy (PWE). The study was conducted in collaboration a group of HCPs caring for PWE, the International Equity in Epilepsy Group (IEEG). The Chi-square test, α=0.05, pairwise multiple comparisons conducted via Bonferroni, α=0.017 were used for data analyses.
Results: Participants were from lower middle-income country (LMIC; n=53), upper-middle income country (UMIC; n-165), high income country (HIC; n=22), and from four regions (Africa 5.6%; Asia 31.2%; Caribbean 12.4%; Latin America 50.8%). Majority of participants were from urban (97.1%) and public health settings (83.2%). The major concern for PWE during the pandemic was difficulty in reaching physicians/healthcare providers (*P*=0.006; HIC <LMIC; HIC< UMIC). There were no significant differences in concerns such as difficulty in getting medication, difficulty reaching and urgent care facility or medication availability in the pharmacy. The major barriers since the pandemic were financial trouble - reduced income/expenses to travel (*P*<0.001; UMIC<LMIC; UMIC<HIC); lockdown (*P*=0.01; UMIC <LMIC); clinic closure (*P*=0.005; UMIC<HIC); long waiting times at clinics (P=0.009; LMIC<UMIC, HIC). No significant differences were found for barriers such as transportation disruption, fear of getting infected with CoV-2 or healthcare worker shortage. Restricted services were lab work (*P*=0.02), EEG, MRI, and CT. The teleconsultation methods used were SMS (*P*=0.01; UMIC <LMIC), social media including WhatsApp, WeChat, Facebook messenger, and telephone calls.
Conclusion: Epilepsy care delivery in resource-poor countries has been affected due to COVID-19. Access to services such as EEG and neuroimaging were heavily impacted and rapid conversion to various methods of teleconsultation required. Such disruptive conditions are often disproportionally felt by many resource-poor countries.

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Implementing American Academy of Neurology (AAN) Quality Measures in Antigua using quality improvement methodology

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Introduction: The AAN has developed quality measures related to various neurological disorders. The latest epilepsy quality measures were published in 2017[1] and for child neurology in 2018.[2, 3] Quality measures are developed based on evidence to support a "care process", however, gaps still exist in implementation. QI methodology is used to facilitate implementation of these quality measures and improve performance.[4, 5]We utilized QI methodology to increase the percent of patients with epilepsy quality measures documented within an outpatient neurology clinic in Antigua.
Methods: To date, there has been no electronic healthcare record (EHR) in the healthcare system in Antigua. Thus, data collection and analysis proves challenging. We utilized the Institute for Healthcare Improvement (IHI) Model for Improvement[6] to develop a Key Driver Diagram. The project was exempt from IRB approval due to being a QI project. The abstract was prepared using the SQUIRE 2.0[7] standards for reporting quality improvement.
Results: Current and future state process maps were developed to determine areas of opportunity for interventions. This served as the frame for key driver creation. Interventions were developed following a "Plan Do Study Act (PDSA) cycle". One intervention was the creation of a RedCap database to be utilized by healthcare providers during clinical patient encounters. Data around quality measures will be de-identified and analyzed to create statistical process control (SPC) charts. The American Society for Quality criteria for centerline shifts[8] will be utilized to determine if significant improvement is noted. A data use agreement was created for data integrity.
Discussion: QI methodology can be used for implementation of quality measures in poor-resource settings to improve patient care outcomes without use of significant resources. Implementation of quality measures can increase efficiency in clinical delivery. Similar QI methodology could be implemented in other resource-limited countries of the Caribbean and globally.

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A novel stereotactic volumetric radiofrequency ablation technique helps in ascertaining 'subtle' epileptogenic zones in difficult-to-treat epilepsy surgery

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Purpose: Uncertainty of the epileptogenic zone despite multimodal pre-surgical evaluation is a difficult epilepsy surgery problem. We sought to evaluate a novel stereotactic volumetric radiofrequency ablation (vRFA) technique to deliver a therapeutic challenge and better delineate the extent of the epileptogenic zone in 'difficult-to-treat' refractory focal epilepsies. In contrast to stereo-EEG (SEEG) electrode based RF thermocoagulation, we used conventional RF ablation probe.
Methods: Patients undergoing the stereotactic vRFA procedure between January 2016 and Jan 2022 and with a follow-up of 6 months were included in this retrospective analysis. The vRFA technique involves stacked RF lesions generated using a conventional RF generator at multiple target points within multiple stereotactic trajectories eventually summating to provide an 'ablative cone' in the cortical regions felt to be epileptogenic after non-invasive and/or invasive evaluations.
Results: Twenty-seven patients underwent vRFA procedures and had a mean follow-up period of 16.7 ± 9.2 months. MRI was negative or subtle in 11 (41 %). 24 patients had SEEG monitoring. Ablative targets were insulo-opercular (7), paraventricular (4), paracentral lobule (3), orbito-frontal (2), cingulate (2), lingual (3), temporo-parietal (2), and cuneus/occipital (4). Seventeen patients (63 %) remained seizure-free on last follow-up. Overall, 20 had a favorable response to vRFA challenge characterized as > 2 months of seizure-freedom. Amongst the seizure-free patients, two were seizure free after resection of ablated area. Ten patients who were not seizure-free on last follow-up did have an initial favorable response. We recorded sensorimotor deficits in 3 (permanent in one), visual field deficits in two, and cognitive deficits in one patient occurred.
Conclusion: Stereotactic vRFA is a minimally invasive thermoablative technique using low-cost conventional RF lesioning hardware that may be useful to test hypothesis in difficult-to-treat epilepsy surgery in low resource countries lacking the expensive laser thermoablative technology. Prospectively, its long term efficacy needs to be ascertained.

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Seizure outcomes in persons with autism spectrum disorder undergoing epilepsy surgery: a systematic review

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Purpose: Autism spectrum disorder (ASD) and epilepsy commonly co-occur. Resective and non-resective surgeries can be effective treatments for patients with drug resistant epilepsy. However, past research in patients with ASD and epilepsy has yielded mixed results in regard to seizure outcomes following epilepsy surgery. We performed a systematic review focused on outcomes of epilepsy surgery in patients with ASD.
Methods: We adhered to the PRISMA standards. Using relevant search terms, MEDLINE, Embase, and PsycInfo were queried from inception to December 2021. Studies were included if they reported seizure frequency following epilepsy surgery in persons with ASD.
Results: 593 abstracts were identified, out of which 78 were selected for full text review. Thirty-seven studies reporting on 292 patients were included. 126 patients underwent resective surgery, 146 underwent neuromodulation (139 VNS, 6 RNS, 1 DBS), and 19 underwent other palliative procedures (15 corpus callosotomy, 4 multiple subpial transection). Outcomes were stratified into four categories based on a combination of Engel classification and percentage seizure reduction at latest follow-up. The distribution of seizure outcomes for all procedures was as follows: 27.74% Engel I or seizure free, 17.12% Engel II or >75% seizure reduction, 21.23% Engel III or 50-74% seizure reduction, 33.56% Engel IV or <50% seizure reduction. Resections resulted in more favorable outcomes compared to VNS neuromodulation (50.79% Engel I vs. 7.91% Engel I, $p = 0.028$).
Conclusion: Based on past work, there is potential for properly selected patients with ASD and epilepsy to experience a significant reduction in seizure frequency or seizure freedom following resective and non-resective epilepsy surgery. While there is a need for more large prospective studies, our review suggests that ASD patients may benefit from surgical treatment.

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MRI negative frontal lobe epilepsy: outcomes of surgical resection and utility of FDG PET in presurgical evaluation

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Purpose: Presently, MRI negative frontal lobe epilepsy represents one of the most challenging frontiers in epilepsy surgery. This study describes the surgical outcome, histopathological findings, and utility of FDG PET in MRI negative frontal lobe epilepsy.
Method: This retrospective study included 35 drug-resistant MRI negative epilepsy patients from a single centre who underwent frontal lobe resection for epilepsy following invasive EEG monitoring. The patients were followed up for at least 12 months postoperatively, and the seizure outcome was classified using Engel's classification of postoperative outcome. Histopathological examination was done for all the patients and was compared to the surgical results of the patients. Correlation of Brodmann area brain atlas mapping between post-resection MRI and pre-resection PET was done in 19 patients.
Results: Eighteen patients (54 %) reported Engel class 1 seizure-freedom. Four (12 %) had Engel class 2 outcome, 6 (18 %) had Engel class 3, and 5 (15 %) had Engel class 4 outcomes. Two patients were lost to follow-up. Twenty-two patients (63 %) showed features of focal cortical dysplasia. Of the seizure-free patients, 13 (76.5 %) had histological evidence of dysplasia, and the remaining 4 (23.5 %) had nonspecific reactive gliosis. We observed that the mean percentage of area of PET hypometabolism included in resection was maximum in the patients with Engel 1 outcome.
Conclusion: This study suggests that post-surgical outcome in MRI negative patients undergoing frontal lobe resection was better when the maximum area of PET hypometabolism was resected during the surgery. The study reiterates that FDG PET is an essential presurgical tool in evaluating MRI negative frontal lobe epilepsy patients. In our cohort, the majority of the seizure-free patients had histopathological evidence of dysplasia.

Neuroimaging

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Whole-brain metabolic pattern analysis in patients with anti-LGI1 encephalitis

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Purpose: Faciobrachial dystonic seizures (FBDS) and hyponatraemia are the distinct clinical features of autoimmune encephalitis (AE) caused by antibodies against leucine-rich glioma-inactivated 1 (LGI1). The pathophysiological pattern and neural mechanisms underlying these symptoms remain largely unexplored.
Methods: We included 30 patients with anti-LGI1 AE and 30 controls from a retrospective observational cohort. We performed whole-brain metabolic pattern analysis to assess the symptomatic networks in FBDS in patients with anti-LGI1 AE. Logistic regression was applied to explore independent predictors of FBDS and Pearson correlation was used to evaluate the functional coupling within brain regions. Finally, we investigated the pathophysiological pattern underlying hyponatraemia and the effects of blood sodium levels on brain network alterations using multiple regression.
Results: The symptomatic network of FBDS mainly involved the Rolandic area, subcortical structures (caudate nucleus and thalamus), and the cerebellum. Hypermetabolism in the cerebellum was an independent predictor of FBDS ($P < 0.01$). Moreover, stronger functional coupling within motor-related brain regions, intra-subcortical structures, and the cerebellum was observed in patients with FBDS. Pathophysiological network analysis of hyponatraemia highlighted a positive effect on thalamus, cerebellum, and white matter.
Conclusions: Our study identified the symptomatic network of FBDS and pathophysiological network of hyponatraemia in patients with anti-LGI1 AE, which may contribute to our understanding of the neural mechanisms underlying FBDS and hyponatraemia-associated effects on the brain and improve future diagnosis and treatment.

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Voxel-based asymmetry analysis of FDG PET improves epileptogenic zone detection

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Purpose: Interictal 18F FDG PET is an important imaging modality to localize the epileptogenic focus in drug resistant epilepsy patients. In this study, we described an automated interhemispheric PET asymmetry analysis technique to detect hypometabolism after anatomical symmetrization.
Method: This study included 19 drug resistant epilepsy patients who underwent PET-MR acquisition for epilepsy presurgical evaluation. All patients were followed-up for > 12 months of postoperative response. Voxel-based asymmetry index of PET was calculated following the interhemispheric anatomical asymmetry correction. The asymmetry index images were converted to z-score and thresholded at z>3, 4 and 5. All patients were analyzed using the described technique and the results were retrospectively validated from the surgical intervention.
Results: We found that 16 of 19 patients with Engel 1 postsurgical outcome had high degree of overlap between the detected hypometabolism (with z>4 threshold) and resection cavity. One patient with Engel 2 and two patients with Engel 3 outcome had no overlap of detected hypometabolism and the resection cavity.
Conclusion: The novel technique of voxel-based PET hypometabolism detection was proved to be efficient in automatically detecting and delineating the PET hypometabolism independent of normative control PET data. Prospectively, this technique may help in planning the intracranial electrode placement or resective surgery for better outcome.

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Statistical asymmetry analysis of volumetric T1 MRI and 18F FDG PET in temporal lobe epilepsy

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Purpose: The volumetric MRI and interictal 18F fluorodeoxyglucose (FDG) PET are the most important imaging modalities in presurgical evaluation of epilepsy. Quantitative analysis may further increase their yield in evaluating temporal lobe epilepsy (TLE). In this study, we statistically analyzed hippocampal volumetry and FDG PET metabolic asymmetry to detect TLE.
Methods: This study included 31 epilepsy patients who underwent resective surgery following the depth electrode implantation in the hippocampus. All patients were seizure free for more than 12 months. Patients were divided into Group I (n=16; temporal lobe resection) and Group II (n=15; extratemporal lobe resection). Amygdala and hippocampus were manually segmented from volumetric T1 MRI. The segmented amygdala and hippocampus along with Brodmann area template were used as regions of interest to determine the mean regional metabolism in PET. ROC (receiver operating characteristic) analysis was used to find a clinically relevant cutoff asymmetry value in hippocampal volumetry and temporal metabolism.
Results: ROC curve analysis identified a hippocampal volume asymmetry of 4.21% with sensitivity of 88.89% and specificity of 100% ($p<0.001$). PET asymmetry analysis revealed the statistically significant asymmetry only in hippocampus and Brodmann area 38 ($p<0.001$). The asymmetry higher than these cutoffs would indicate the temporal lobe seizure onset.
Conclusion: Using statistical asymmetry analysis, we derived the cutoff asymmetry values to evaluate the hippocampal volumetry and FDG PET. This technique strengthened the utility of MRI and PET in non-invasive detection and exclusion of TLE. The derived threshold parameters warrant further validation in prospective studies.

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Homotopic coupling in persons with focal epilepsy using movie-driven and resting-state fMRI

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Purpose: In addition to the dysfunction of a single pathological area, temporal lobe epilepsy can be considered a network disorder (Pittau & Vulliemoz, 2015), manifesting as abnormal functional coupling between areas. In the human brain, the strongest coupling is typically observed between homologous areas in the two hemispheres, and the corollary of strong coupling is high sensitivity to abnormality. Accordingly, in persons with refractory focal epilepsy, we evaluated how functional coupling activity between homotopic brain areas manifested in both resting-state and movie-driven fMRI.
Method: 22 persons with epilepsy (PWE) and 24 healthy controls were scanned using fMRI at rest and while watching a brief and engaging film clip. Registration and surface-based parcellation (Glasser et al., 2016), was used to identify 180 cortical regions and 22 functionally distinct sections in each participant. Homotopic coupling activity between pairs of regions and sections in a subset of controls was calculated to be used as a set of normative distributions, and activity in PWE and controls that fell outside 2 SD of the mean for each region/section was defined as abnormal. The number of abnormalities and the strength of coupling activity was compared between groups and scanning paradigms.
Results: PWE displayed more abnormal homotopic coupling activity compared to controls (p = .006), and the combined effects from resting-state and movie-driven fMRI contributed to this significance. PWE displayed unique patterns of abnormal homotopic coupling within and outside of the temporal lobe. Differences in the strength of homotopic coupling activity between movie-viewing and resting-state were identified in the inferior parietal, medial temporal and early auditory and visual cortices.
Conclusion: Variation in the degree and location of homotopic coupling abnormalities between scanning paradigms demonstrates that the combined use of movie-driven and resting-state fMRI enables a comprehensive evaluation of functional connectivity in refractory temporal lobe epilepsy.

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Investigation of social cognitive processes among adolescents with epilepsy

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Purpose: Adolescents with epilepsy (AWE) exhibit impairments in social behaviour; however, the processes underlying these deficits, such as social cognition, have been largely unexplored. Social cognition encapsulates the cognitive abilities involved in accurately processing and interpreting social information and includes emotion recognition, cognitive empathy/theory of mind (understanding others' emotional/mental states), and emotional empathy (experiencing the affective states of others). The objective of this study was to delineate social cognitive processes among AWE.
Method: AWE (n=30) were recruited from The Hospital for Sick Children and Canadian community epilepsy support centers. Friends and/or cousins of AWE were recruited as controls (n=16). Participants completed two tasks; 1) a face emotion task to evaluate recognition of anger, disgust, happiness, fear, and sadness, at three different emotional intensity levels (100%, 70%, 40%); 2) an adolescent-adapted Multifaceted Empathy Task to index cognitive and emotional responding to positive and negative emotional pictures. The Peabody Picture Vocabulary Test was administered to estimate intellectual functioning and language comprehension. All study measures were completed online with the researcher.
Results: Collapsed across emotional intensity levels, AWE recognized sad faces less accurately than controls, (mean accuracy difference= 8.52%, $t(44)=2.08$,$p=0.04$). For each emotion, the difference between groups was consistent across each intensity level. AWE and controls reported similar cognitive and emotional empathy ratings.
Conclusion: AWE have difficulty recognizing the emotion of sadness as depicted in facial expressions. We will continue to recruit more participants to determine whether this result holds in a larger sample, and whether this difficulty is related to social behaviours. The results can be used to prepare caregivers and educators for the specific social cognitive challenges in AWE. With this knowledge, specific interventions and educational plans can be created to better accommodate and strengthen these areas of dysfunction.

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Illness representation and self-management in adolescents with functional seizures

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Purpose: Adolescents with functional seizures (nonepileptic seizures attributed to stress) miss more school, experience more academic challenges, and have poorer quality of life than healthy counterparts. To understand disparities, researchers must understand adolescents' interpretation of their condition and self-management. Illness representation (IR) is one's interpretation of a health threat that triggers self-management actions and evaluation of self-management effectiveness. IR includes five domains: identity, timeline, consequences, cause, and control. The purpose of this qualitative study was to explore the presence of IR domains within adolescents' descriptions of functional seizure self-management and identify potential relationship patterns with self-management strategies and perceived effectiveness.
Method: Ten adolescents (12-19 years old, 100% female, 80% White) with functional seizures from across the United States were recruited via Facebook support groups. Semi-structured interviews were conducted and recorded using Zoom, transcribed, and coded using deduction and magnitude coding according to IR domains, self-management strategies, and perceived self-management effectiveness.
Results: Out of 135 IR meaning units, most pertained to condition consequences (41), identify (39), and cause (31); far fewer related to controllability (15) and timeline (9). For adolescents expressing some sense of control (vs. no control), none expressed an expectation of seizure freedom, all had a proactive plan deemed effective, and 80% had a reactive plan deemed effective. For adolescents expressing no control, 25% expressed seizure freedom was possible, all had a proactive plan deemed effective, and none had a reactive plan deemed effective.
Conclusion: Too few adolescents expressed understanding potential seizure freedom. A potential relationship pattern between controllability and use of effective reactive strategies was noted. These study findings suggest adolescents require greater understanding of condition timeline and controllability, which may improve self-management and perceived self-management effectiveness. Knowledge gained will inform future functional seizure self-management surveys and interventions for improved academic, health, and quality of life outcomes.

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Influence of prebiotics on ketogenic diet induced seizure protection in a model of pediatric epilepsy

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Purpose: The ketogenic diet (KD) is an effective treatment for refractory epilepsy, especially in young infants. Nevertheless, KD has implications for somatic growth, development, and gut microbiota. The purpose of this study was to examine the impact of adding a prebiotic to a KD formula in a validated rodent model of infantile spasms syndrome (IS).
Method: Here, we tested the impact of incorporating a prebiotic fiber (oligofructose-enriched inulin, Orafti Synergy 1 (PRE); 0.8g/dL formula) into a KD diet (4:1 ratio by weight of fat to carbohydrate+protein) on seizures, developmental milestones, fecal microbiota, circulating and tissue metabolites, and hippocampal mitochondrial metabolism in a well-established rat model of IS. Following seizure induction, animals were randomized to KD or KD+PRE diets. A third group without seizure induction and suckled by dams was included as a normally developing reference group.
Results: The KD and KD+PRE diets were well tolerated. PRE inclusion had no impact on seizures despite a decrease in blood ketones and an increase in circulating glucose. No differences in developmental milestones (i.e., surface righting, negative geotaxis, and open field behavior) were observed between KD and KD+PRE groups, except ultrasonic vocalizations that were more frequent in KD+PRE. In the liver, PRE increased triglyceride concentrations, decreased carnitine levels, and downregulated genes encoding enzymes responsible for ketogenesis. In the hippocampus, KD+PRE increased glutathione levels but did not affect the maximal respiratory capacity of mitochondria. Microbiota analysis showed that KD+PRE treatment increased microbial richness and relative abundances of *Bifidobacterium pseudolongum*and*Lactobacillus johnsonii*.
Conclusion: Given the importance of the early-life gut microbiome, adding PRE to a KD may protect beneficial bacteria in IS.
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Targeted gut microbiota manipulation attenuates seizures in a model of infantile spasms syndrome

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Purpose: Infantile spasms syndrome (IS) is an early-onset epileptic encephalopathy. As IS can be refractory to antiepileptic medication, the ketogenic diet (KD) is often employed to control seizures. Since KD effectiveness is dependent on the gut microbiota, we examined whether a targeted probiotic, mimicking changes induced by the KD would be effective in mitigating seizures.
Method: The KD was administered to rodents modeling symptomatic IS. Seizure reduction was examined in relation to KD-induced gut microbiota changes. To test the dependency of these alterations on the gut microbiota, broad spectrum antibiotics were administered. Results of these studies were then used to design a targeted probiotic for IS. Key outcomes included seizures, gut microbiota, developmental milestones, serum and hippocampal metabolomics profiling.
Results: Seizure frequency was reduced by the KD and was associated with microbial alterations including *Streptococcus thermophilus.*Broad-spectrum antibiotic administration further reduced seizures and examination of the fecal microbiota revealed increases in *Lactococcus lactis*and*S. thermophilus.*As both treatments reduced seizures, we created a correlation matrix to explore similarly altered gut microbes following treatment. Administration of *S. thermophilus*and*L. lactis*in a 5:1 ratio reduced seizures and improved locomotor activities in control diet-fed animals, similar to KD-fed animals. Probiotic administration also increased antioxidant status and decreased pro-inflammatory cytokines.
Conclusion: Results suggest that a targeted probiotic reduces seizure frequency and improves locomotor activity in a rodent model of IS and provides new insights into microbiota manipulation as a therapeutic avenue for pediatric epileptic encephalopathy.
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Higher graded doses of a small-molecule TrkB-antagonist improve the PB-efficacy and safety in a neonatal mouse model of refractory seizures

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Purpose: Phenobarbital (PB) resistance poses serious challenge in clinical management of perinatal ischemic stroke-associated seizures. ANA-12, a TrkB antagonist, improved PB-efficacy from ~0% to ~36% seizure suppression at 5mg/kg dose when given as single injection post ischemia with standard loading dose of PB (25 mg/Kg ip) at P7. For achieving FDA clinical trials standards of ~80% or higheranti-seizure efficacy rate, graded doses of ANA12 (10 and 20 mg/Kg as compared to 5 mg/kg ip) were tested in a cohort of CD-1 pups of both sexes to determine optimal combination therapy with PB. Half of standard loading PB-dose was tested with optimal ANA12 dose for additional benefit of reducing PB adverse effects on neonatal brain. Additionally, neurodevelopmental reflexes, ability to thrive, neuronal cell death were accessed.
Method: Following right common carotid ligation, pups were randomly injected with different graded doses of ANA12 post ischemia and standard loading dose of PB at P7 1 hour after insult. Developmental milestones were determined using negative geotaxis and righting reflex tests from P7-P14. Flurojade staining compared neuronal cell death associated with unilateral ligation in brains harvested 24 hours after ischemic insult.
Results: The intraperitoneal dose of 10mg/Kg ANA12 in combination with PB significantly reduced seizure burden and improved seizure suppression with plateauing of anti-seizure responses at 20mg/Kg ANA12. ANA12*per se* showed no significant changes in neurodevelopmental reflexes and weight gain. Neuronal cell death associated with unilateral ligation increased Flurojade-positive cells in right cortex and left striatum in anterior and posterior brain sections, attenuated by combination of 10mg/Kg ANA10+PB in right cortex in anterior section of brain.
Conclusions: A single 10 mg/Kg ip dose of ANA12 improved PB-efficacy and safety in comparison to 5 mg/Kg ip in neonatal model of PB-refractory seizures. ANA12 at 20mg/Kg showed no additional therapeutic benefit over 10mg/Kg ip.

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Epilepsy phenotype in a large cohort of neonatal arterial ischemic stroke (NAIS) and presumed perinatal arterial ischemic stroke (PPAIS)

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Purpose: To study the epilepsy outcomes in a large cohort of neonatal arterial ischemic stroke (NAIS) and presumed perinatal arterial ischemic stroke (PPAIS).
Methods: This was a hospital-based retrospective cohort study. Children aged less than 18 years with NAIS and PPAIS were included. Children with concurrent hypoxia, cerebral venous thrombosis or parenchymal haemorrhage and those who do not have complete records were excluded. Outcomes included proportion of children who developed epilepsy, infantile spasms (IS) and drug-resistant epilepsy (DRE) later in life. A total of 96 patients were enrolled.
Results: 43(44.7 %) had NAIS and 53 (55.2 %) had PAIS. 55 (57.2 %) were males and 41 (42.7 %) were females. The mean age at last follow-up was 14 years. The most common arterial territory involved was MCA (88.9%) and there was left preponderance (64 %). The most common etiology for stroke was presumed placental embolism seen in 63 %. Among the NAIS group, the most common presentation of stroke was seizures (86.8 %), with the most common type being asymmetric-clonic (61.8 %). Among the PPAIS group, seizures were the first presenting symptom in 7 (11.7%). Twelve patients (28%) developed epilepsy following NAIS later in life. 27 (49 %) of those in the PPAIS group had epilepsy. Focal epilepsy was the most common epilepsy syndrome following PPAIS/NAIS. IS was seen in 9 (23%) patients who developed epilepsy, and epileptic encephalopathy with continuous spike-wakes in slow-wave sleep was seen in 5 (12.8%) patients. DRE was seen in 5 (12.8%) patients among those who developed epilepsy. Three children underwent hemispherectomy with all achieving ILAE Class I outcome.
Conclusion: This study shows that epilepsy in later childhood is seen in one-third of children with NAIS and 49 % of those with PPAIS, with 23 % developing IS and 12.3 % developing DRE.

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Correlation between interleukin–6 and the risk of developing seizures in hospitalized patients with COVID-19: case-control study

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Purpose: Prominent effects of SARS-CoV-2 infection on the nervous system including convulsive disorders have been particular focuses of interest. Increased levels of IL-6 can be one of the main contributors to this acute manifestation. We aimed to investigate the correlation between this cytokine and the risk of developing seizures. Studies that already have been conducted found the correlation between the severity of COVID-19 and IL-6 Levels, but its association with specific complications remains unclear.
Method: In early December we conducted a case-control study on the patients with PCR confirmed SARS-CoV-2 Infection. 50 patients who developed seizures have been chosen (Cases) to assess IL-6 values compared to those (50 patients) who did not (Controls). Statistical data were analyzed based on IBM-SPSS 26, using an unpaired t-test. To avoid potential bias, gender and age difference between these 2 groups were minimized, cases with severe comorbidities were excluded.
Results: The mean value of IL-6 level among controls was 13.290 (+/- SD 13.290, SEM 1.698), while the same value among cases was 23.400 (+/- SD 11.798, SEM 2.638). The two-tailed p=0.0026. The mean of Control minus Case equals -10.110.95% confidence interval of this difference: From -16.461 to -3.759. t=3.2224. df=38. Standard error of difference=3.137.
Conclusions: The mean value of IL-6 was 1.76 times greater in patients who developed seizures compared to those in the control group. Although we could not identify the relationship between the clinical severity of convulsion and IL-6 levels, it was still associated with a relatively increased risk of developing this complication. This correlation could be important not only in terms of seizures but other neurological and non-neurological complications as well, emphasizing the need for further investigation of individual clinical sequels associated with COVID-19.

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A portrait of patients with psychogenic nonepileptic seizures seen at the Montreal Neurological Hospital Epilepsy Monitoring Unit (EMU)

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Purpose: Psychogenic non-epileptic seizures (PNES) can be definitively diagnosed upon recording typical events with video-EEG. We describe clinical characteristics of patients admitted to our EMU for diagnostic clarification.
Method: We reviewed discharge summaries listing PNES as discharge diagnosis randomly sampled from May 2017 to July 2021.
Results: We reviewed 44 patients (84% female) aged 17-89y at time of diagnosis (mean=38.0 ± 16.6) and 14-88y at symptom onset (31.4 ± 17.0). Twenty-five (57%) were on ≥ 2 anti-seizure medications on admission (mean treatment duration 8.1 ± 10.8 years). Twenty-one (48%) patients had comorbid epilepsy and PNES, whereas 18 had PNES alone. In 5 patients, epilepsy could not be ruled out. Thirteen had a history of mild traumatic brain injury. Six had family history of epilepsy, 4 of whom had PNES alone. Eleven patients had a history of sexual abuse and 7 had been physically abused. Twenty-one patients had psychiatric diagnoses: anxiety/depression (N=15), ADHD (N=5), PTSD (N=5), cluster B (N=3). Mean length of stay was 7.0±3.2 days. Sixteen patients (13 with comorbid epilepsy) had ≥ 2 admissions, mostly for altered event frequency or type. Semiology was often hyperkinetic (N=28) with preserved awareness (N=18).
PNES began at age ≥ 60 in 4 patients (1 with comorbid epilepsy and 3 with multiple medical comorbidities). Chemotherapy initiation was associated with PNES onset in 1 cancer patient. The other three patients had childhood traumatic experiences.
Conclusion: Our pilot study highlights a small subgroup of patients with late-onset PNES. Whereas one patient had an identifiable trigger immediately preceding PNES symptoms, onset in the other three was very late considering their risk factors from childhood. Additionally, the observed delay from symptom onset to diagnosis confirmation imposes significant burden on patients and must be improved. Whereas video-EEG monitoring is required for definitive PNES diagnosis, limited EMU resources remain mostly allocated for management of drug-resistant epilepsy patients across centres.

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Examining the impact of driving restrictions on patients with epilepsy in Ireland

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Purpose: Driving restrictions have a significant impact on patients with epilepsy and their families. This is documented in international studies but has not been reported in an Irish context. The goal of this study is to examine this impact on an Irish based tertiary hospital cohort.
Method: Patients were recruited through the Beaumont Hospital neurology service after informed of driving restriction secondary to an epileptic seizure. Patients were subsequently contacted by phone and interviewed using a standardised proforma.
Result: Our analysis includes 20 patients interviewed (female 70%, mean age: 40.5 years). Forty percent of patients (n=8) had received a driving restriction for the first time, due to a new diagnosis of epilepsy.
Ninety-five percent (n=19) reported a car as their primary mode of transport prior to driving restriction, the single additional patient reporting using public transport. During restriction, 60% (n=12) continued to primarily use a car driven by a friend or family member. Fifteen percent (n=3) of patients switched from personal car to using public transport. Eighty-five percent (n=17) reported access to public transport.
Thirty-five percent (n=7) reported that their transportation options were limited by cost, while fifty-five percent (n=11) reported being negatively affected financially and 15% (n=3) were forced to give up their job. Fifteen percent (n=3) reported a negative impact on the doctor-patient relationship, 5% (n=1) had sought a second opinion and 10% (n=2) of patients admitted to driving during the restriction.
Conclusions: Personal car is the primary mode of transport in this cohort both before and after driving restriction. The majority of patients adhered to the law and did not report a breakdown in the relationship with their doctor. Access and cost of public transport, reliance on family and financial loss are significant factors affecting patients.

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Impact of the 2021 North American winter storms on children with epilepsy

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Purpose: In February 2021 a series of winter storms caused power outages for nearly ten million people in the USA, Mexico and Canada. In Texas, the storms caused the worst energy infrastructure failure in the history, leading to shortages of water, food, and heat for nearly a week. The reported death toll was 246, and 10% of deaths were attributed to exacerbated pre-existing illnesses. Children with epilepsy (CWE) are particularly vulnerable to running out of medications due to disruptions in the supply chain. We aimed to determine the impact of the winter storm on our patient population of CWE.
Methods: We performed a survey of families with CWE about the impact of the 2021 winter storm.
Results: 101 families completed our survey. 24/101 (23.8%) reported daily seizures at baseline, and 63/101 (62.4%) stated to have been affected by the storm. 34/101 (33.7%) were without power and 33/101 (32.7%) without heat for >24hrs. 19/101 (18.8%) lacked food, and 17/101 (16.8%) drinking water. 25/101 (24.8%) needed to refill antiseizure medications, and 17/25 (68%) reported difficulties refilling medications. Reasons were dangerous road conditions (11/17, 64.7%), closed pharmacies (11/17, 64.7%), and/or delayed shipments (9/17, 52.9%). 9/101 (8.9%) completely ran out of antiseizure medications as a result of not being able to refill, 5/9 (55.6%) had an increase in seizure frequency or duration, and 2/9 (22.2%) went to the emergency room as a result of increased seizures after running out of medications.
Conclusion: Our results demonstrate that close to 10% of our patients ran out of antiseizure medications, and many more were affected by lack of water, heat, power and food. This shows the vulnerability of children with epilepsy in the event of a large-scale infrastructure failure and emphasizes the need for adequate and appropriate disaster preparation despite fiscal resources.

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