Epilepsy Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

ADHD = attention-deficit/hyperactivity disorder;
AUC = area under the receiver-operating characteristic curve;
ED/EMS = emergency department/medical service;
LAEP = Liverpool Adverse Event Profile; **SV2A** = synaptic vesicle glycoprotein;
VGSC = voltage-gated sodium channel.

Welcome to issue 15 of Epilepsy Research Review.

We begin this issue with research from colleagues in Melbourne who have used seizure and heart rate cycle data recorded by a smartwatch to forecast seizure risk. There are also two studies looking at risks associated with prenatal or fetal antiseizure medication exposure, and another reporting on the impact of suspected epileptic seizures on emergency services in Finland. We conclude the issue with another research paper from Australia, this one evaluating the efficacy and tolerability of add-on brivaracetam in adults with epilepsy in a real-world setting.

We hope you enjoy this update in epilepsy research. As always, all comments and feedback you wish to send us are gratefully appreciated.

Kind Regards,

Professor Mark Cook AO
mark.cook@researchreview.com.au

Forecasting seizure likelihood from cycles of self-reported events and heart rate

Authors: Xiong W et al.

Summary: These Australian researchers sought to validate a method for forecasting seizures that used seizure and heart rate cycle data recorded by devices worn by 13 participants for a mean of 562 days, during which a mean of 125 self-reported seizures were recorded to a smartphone app. The best forecasts achieved a mean AUC of 0.73 for nine of the participants, demonstrating performance greater than chance during retrospective validation. A prospective evaluation of long-term data for six of the participants after algorithms were developed revealed a mean AUC of 0.77 for subject-specific forecasts, with performance greater than chance in four participants.

Comment: Accurate seizure forecasting has long been the ambition of many researchers, achieved previously with invasive implantable systems. The proliferation of wearable devices and their ability to collect multidimensional physiological data provided the opportunity to examine alternative methods. The study examined the ability of wearable systems and diaries to forecast seizures, using a combination of patient-reported events and cardiac data to provide a risk forecast. They demonstrated for a number of participants that successful seizure forecasting could be achieved. The study shows the potential of wearable devices in this area, and whilst they lack the resolution of implanted systems, they may still provide useful clinical information to guide investigations and management.

Reference: eBioMedicine 2023;93:104656
Abstract

Epilepsy Research Review™

Independent commentary by Professor Mark Cook AO

Professor Mark Cook is Director of The Graeme Clark Institute, The Sir John Eccles Chair of Medicine and Director of Clinical Neurosciences at St. Vincent's Hospital. Professor Cook specialises in the treatment of epilepsy. He is recognised internationally for his expertise in epilepsy management, particularly imaging and surgical planning. After completing specialist training in Melbourne, he undertook an MD thesis while working as Brain Research Fellow at Queen Square, London. He returned to St. Vincent's Hospital, Melbourne to continue his interest in management of complex epilepsy. He has worked closely with engineers for most of his career, developing novel therapies for epilepsy. His interests have included experimental models of epilepsy and seizure prediction, and he has led the commercialisation of an implantable seizure detection device now in clinical trials.

Adverse event profiles of antiseizure medications and the impact of coadministration on drug tolerability in adults with epilepsy

Authors: Willems LM et al.

Summary: These researchers used the LAEP (Liverpool Adverse Event Profile) to identify adverse event profiles of antiseizure medications and evaluate the impact of coadministered drugs on adverse events using retrospective data from 486 participants from a large German study. It was found that the adverse event profiles of antiseizure medications, both for categories and individual agents, were similar to those reported in the literature. Adverse event profiles were favourable for SV2A (synaptic vesicle glycoprotein) and VGSC (voltage-gated sodium channel) modulators, and the profile for brivaracetam was better than that for levetiracetam with regards to psychobehavioural adverse events. The only independent predictors of high LAEP values, in addition to seizure frequency, were AMPA modulators and antidepressants. Correlations between LAEP and antidepressants were significantly lower than those between LAEP and Hospital Anxiety and Depression Scale and Neurological Disorders Depression Inventory for Epilepsy. Artificial neural network analyses revealed that perampanel, zonisamide, topiramate and valproic acid were important nodes, whereas VGSC and SV2A modulators had low relevance for predicting adverse events; in addition, cardiovascular agents, analgesics and antipsychotics were important coadministered agents.

Comment: Much of clinical epileptology is concerned with the right medication for the right patient, not only with regard to efficacy, but also tolerability. The study here describes the adverse events across a large number of patients relating to various categories of newer antiseizure medications, finding that the SV2A modulators, as well as the sodium channel modulators (including lamotrigine), were better tolerated than others, and that perampanel in particular was less well tolerated. Not unexpectedly they found that brivaracetam was better tolerated than levetiracetam in patients with psychiatric adverse events related to that agent.

Reference: CNS Drugs 2023;37:531–44
Abstract

Evaluation of the feasibility, diagnostic yield, and clinical utility of rapid genome sequencing in infantile epilepsy (Gene-STEPS)

Authors: D'Gama AM et al.

Summary: The feasibility, diagnostic yield and clinical utility of rapid genome sequencing for patients with epilepsy with an onset at age <12 months were explored in a pilot cohort study of 100 such patients from Australia, Canada, the UK and the US; their median age of seizure onset was 128 days. Genetic diagnoses could be identified in 43% of the cohort, with a median time from seizure onset to rapid genome sequencing result of 37 days. There were significant associations of genetic diagnosis with: i) neonatal versus infantile seizure onset (74% vs. 36% [p=0.0027]); ii) intensive care versus nonintensive care and outpatient settings (71% vs. 44% and 28%, respectively [p=0.0178]); and iii) self-limited epilepsies versus developmental and epileptic encephalopathies or other syndromes (87% vs. 35% [p=0.001]). Rapid genome sequencing implicated 34 unique genes or genomic regions. Genetic diagnoses had immediate clinical utility, informing treatment in 56% of evaluable cases, additional evaluation in 65%, prognosis in 86% and recurrence risk counselling in 100%.

Comment: Rapid genome sequencing has much to offer in the early assessment of infantile epilepsy particularly, and this study demonstrated the utility of the process in a large international study. Importantly, they demonstrated the genetic diagnosis had significant clinical utility, informing treatment, leading to additional evaluation, and leading to useful prognostic information in a very large proportion of all patients.

Reference: Lancet Neurol 2023;22:812–25
Abstract

Cognitive outcomes at age 3 years in children with fetal exposure to antiseizure medications (MONEAD study) in the USA

Authors: Meador KJ et al., for the MONEAD Investigator Group

Summary: The impact of fetal exposure to commonly used antiseizure medications on neuropsychological outcomes at age 3 years was explored in this prospective, observational cohort study enrolling women with (n=351) and without (n=105) epilepsy during pregnancy and their children. There was no significant difference between children born to women with epilepsy (n=345) and those born to women without epilepsy (n=106) for Verbal Index score at age 3 years (adjusted least-square mean, 102.7 vs. 102.3), with factors significantly associated with a reduced score being maternal intelligence quotient, maternal education, postbirth anxiety, gestational age at enrolment, child's sex and child's ethnicity. There was no significant effect of antiseizure medication exposure on Verbal Index score for maximum third trimester blood concentrations, but secondary analyses revealed exposure-dependent effects on multiple cognitive measures, with variation by medication.

Comment: There has been significant concern about the neurodevelopmental effects of antiseizure drugs when administered during pregnancy, with problems related to some of the older agents in particular highlighted in recent years. This study examined a large group of women with and without epilepsy, examining the cognitive effects of some of the newer anticonvulsants, chiefly levetiracetam and lamotrigine, on neurodevelopmental outcomes at 3 years of age to those exposed *in utero*. The researchers found no difference in neurodevelopmental outcomes, although a secondary analysis demonstrated perhaps a small negative effect with the use of levetiracetam, but this was less certain. Overall these are very reassuring data, and the authors noted also that there were no effects on cognitive outcomes from breastfeeding while taking these antiseizure medications.

Reference: Lancet Neurol 2023;22:712–22
Abstract

Prenatal exposure to antiseizure medication and incidence of childhood- and adolescence-onset psychiatric disorders

Authors: Werenberg Dreier J et al.

Summary: Associations of prenatal antiseizure medication exposure with psychiatric disorders in childhood and adolescence were examined in a prospective Nordic population-based register of 38,661 singleton children born to mothers with epilepsy. Compared with unexposed children, those with prenatal antiseizure medication exposure (n=16,458) had a higher cumulative risk of the combined psychiatric endpoint of 13 individual disorders by age 18 years (42.1% vs. 31.3%; adjusted hazard ratio 1.80 [95% CI 1.60–2.03]), driven mainly by disorders within the neurodevelopmental spectrum; when analysed by individual medications, topiramate and levetiracetam were significantly associated with ADHD (2.38 [1.40–4.06] and 1.78 [1.03–3.07], respectively), and levetiracetam was also significantly associated with anxiety (2.17 [1.26–3.72]).

Comment: The risks of psychiatric disorders in childhood and adolescence as a complication of exposure to antiseizure medications are little explored, but this Scandinavian study looks at a very large number of patients and found that there was risk, not only with valproate but also with some other medications particularly to topiramate for ADHD and levetiracetam for anxiety. Lamotrigine, carbamazepine and oxcarbazepine seemed relatively safe. These are additional hazards for clinicians to consider when counselling women with epilepsy looking to pregnancy.

Reference: JAMA Neurol 2023;80:568–77
Abstract

Association of mortality and risk of epilepsy with type of acute symptomatic seizure after ischemic stroke and an updated prognostic model

Authors: Sinka L et al.

Summary: These researchers compared mortality and epilepsy risk after different types of acute symptomatic seizures for a derivation cohort of 4552 adult participants from seven cohort and two case-control studies with ischaemic stroke and no prior seizures, with replication in three cohorts of adults with acute symptomatic status epilepticus after ischaemic stroke. Acute symptomatic seizures occurred in 5% of the derivation cohort, with 0.2% presenting with status epilepticus. The 10-year mortality rate was higher for patients with acute symptomatic status epilepticus than for those with short acute symptomatic seizures and those without seizures (79% vs. 30% and 11%, respectively), as was the 10-year risk of epilepsy among those who survived their stroke (81% vs. 40% and 13%). The respective 10-year risks of mortality and epilepsy were 76% and 88% in a replication cohort of 39 individuals with acute symptomatic status epilepticus after ischaemic stroke. When type of acute symptomatic seizures was included as a covariate in the SeLECT 2.0 prognostic model, cases at high risk of poststroke epilepsy were captured.

Comment: The risk of seizures poststroke remains an important issue, and this study looked at predictors of ongoing seizures poststroke. The authors found that patients who suffered status epilepticus had a quite high risk, not only of recurrence of seizures, but a much more significant 10-year mortality, when compared with those who had short, acute symptomatic seizures, and of course compared with those who didn't have seizures. The authors provide data around the use of a prognostic model (SeLECT 2.0 prognostic model), which allows the recognition of high-risk cases and which may allow decisions around therapy for patients who might be found to have a higher risk. Interestingly, they also found that antiseizure medication therapy after acute symptomatic seizures was independently associated with reduced mortality, for reasons that are as yet unclear.

Reference: JAMA Neurol 2023;80:605–13
Abstract

Predictive power of interictal epileptiform discharges in fitness-to-drive evaluation

Authors: Krestel H et al.

Summary: The impact of interictal epileptiform discharges on driving ability was evaluated in patients with various forms of epilepsy using simple reaction tests and a driving simulator. Compared with generalised atypical interictal epileptiform and focal interictal epileptiform discharges, generalised typical interictal epileptiform discharges were associated with significantly longer reaction times by 164 vs. 77 and 48.0 msec, respectively ($p<0.01$) and a higher probability of a session miss/crash (14.7% vs. 0% [$p<0.01$]). Long repetitive bursts of focal interictal epileptiform discharges that lasted for >2 sec had a miss/crash probability of 2.6%. Reaction time prolongation was able to predict cumulated miss/crash probability – a reaction time of 90.3 msec predicted 20% of misses/crashes. All the tests were nonsuperior to each other for detecting miss/crash probabilities and reaction time prolongations. Compared with normal EEG, interictal epileptiform discharges increased the likelihood of a simulated miss/crash by 4.9-fold. The full article provides a table of expected reaction time prolongations and miss/crash probabilities for interictal epileptiform discharges according to type and duration.

Comment: Determining safety to drive is a very significant part of every neurologists clinic activity when assessing patients with epilepsy, and this interesting study examined the effect of interictal discharges on the risk of driving errors or collisions. The researchers did this using a simulations study, finding, perhaps not surprisingly, that generalised discharges of typical type are the primary cause of problems, whereas even long focal interictal and atypical generalised epileptiform bursts carry a lower risk. They liken these increased risks to those of sleepiness or low blood alcohol levels. They provide a guide around the relevance of delayed reaction time, and its likely impact, showing that a reaction time prolongation at 90.3 msec is a clinically relevant effect. This could potentially present a more efficient way of guiding driving assessment in patients with epilepsy, particularly those with typical generalised syndromes with frequent interictal discharges.

Reference: Neurology 2023;101:e866–78
Abstract

Burden of suspected epileptic seizures on emergency services

Authors: Kämppi L et al.

Summary: The burden of suspected epileptic seizures on emergency care was explored in this retrospective, cross-sectional, population-based, 2015–2018 study conducted at a single dispatch centre, a university hospital-affiliated EMS and five EDs in Finland. The 14,364 EMS callouts for suspected epileptic seizures during the study period accounted for 3.3% of all callouts, and 63.4% of these cases were transported to hospital with 23.4% discharged on scene. During the study, there were also 11,493 seizure-related ED visits by 6969 individuals, which accounted for 3.1% of neurology- and internal medicine-related ED visits and there were 4607 hospital admissions with a median length of stay of 3 days. Males accounted for 64.7%, 60.0% and 56.2% of EMS callouts, ED visits and hospital admissions, respectively. The respective overall incidences of seizure-related EMS callouts, ED visits and hospitalisations were 333, 266 and 107 per 100,000 inhabitants, and the total estimated costs were €6.8 million per year, i.e. 0.5% of all specialised healthcare costs within the study area.

Comment: Seizures are an important cause of hospital ED visits, and this study highlights the frequency and overall burden on the health system resulting. Seizures were the cause of 3.3% of EMS calls, and 3.1% of ED visits, and I was surprised it was not more. The study is of adult patients only however, and shows these admissions are responsible for 0.5% of specialised healthcare costs.

Reference: Eur J Neurol 2023;30:2197–205
Abstract

Perampanel for the treatment of people with idiopathic generalized epilepsy in clinical practice

Authors: Trinka E et al.

Summary: The PERMIT study examined real-world perampanel use in 554 patients with idiopathic generalised epilepsy from 17 countries. The respective 3-, 6- and 12-month perampanel persistence rates were 92.4%, 85.5% and 77.3%, and the respective total responder and seizure freedom rates at last visit were 74.2% and 54.6% (81.2% and 61.5% for generalised tonic-clonic seizures, 85.7% and 66.0% for myoclonic seizures, and 90.5% and 81.0% for absence seizures). The overall incidence of adverse events was 42.9%, including irritability (9.6%), dizziness/vertigo (9.2%) and somnolence (6.3%), resulting in a 12-month treatment discontinuation rate of 12.4%.

Comment: Perampanel is increasingly seen as a drug with significant utility in the therapy of generalised epilepsies, and this study provides further evidence supporting its efficacy and tolerability in that setting. It seems to have significant efficacy in all types of generalised seizure patterns, including myoclonus and absence. Adverse events were as expected, particularly with irritability and dizziness, but these were generally at relatively low levels, and discontinuation over 12 months was approximately 12%, so overall tolerability is pretty reasonable and comparable with many other agents. It confirms findings from earlier clinical trials.

Reference: Epilepsia 2023;64:2094–107
Abstract

The efficacy and tolerability of adjunctive brivaracetam for the treatment of adult epilepsy

Authors: Halliday AJ et al., the Australian Comprehensive Epilepsy Centres Consortium

Summary: The efficacy and tolerability of add-on brivaracetam was evaluated in a real-world retrospective cohort of 228 adult attendees of 11 Australian epilepsy centres during 2017–2020; 82.5% had focal epilepsy, and they had received a median of four prior antiseizure medications and two concomitant antiseizure medications. Complete-case, last observation carried forward and intent-to-treat analyses returned respective 12-month response rates of 46.3%, 39.5% and 15.4%, and 12-month seizure freedom rates of 23.9%, 24.6% and 7.9%. Sedation or cognitive slowing was the most frequent adverse effect (14.5%), followed by irritability or aggression (7.0%) and low mood (6.1%). Continuous outcome definitions and 'personalised' outcome assessment timepoints returned similar outcomes. Early responses were durable, with the respective 3-month response and seizure freedom rates of 83% and 85% maintained at all subsequent timepoints. Similar outcomes were seen for focal and generalised seizure subgroups, and also in refractory patients, and although they were worse for patients who were considered highly refractory, brivaracetam was still of some benefit with 12-month seizure freedom rates of 3.2–8.3% (depending on analysis type).

Comment: Real-world data about the efficacy of new antiseizure agents is probably still the most relevant to clinical practice, and this useful study describes the efficacy and tolerability of adjunctive brivaracetam in a multisite Australian study. The authors found that almost 24% of subjects had 12 months of seizure freedom, with the most frequent adverse effects as expected, sedation and cognitive slowing. Irritability and aggression were relatively infrequent. Importantly, early responses with seizure improvement were maintained in the longer term. Findings were similar in those with focal and generalised epilepsies. The study confirms the utility of this agent in a broad range of settings, and the durability of its effect.

Reference: Epilepsy Behav 2023;145:109287
Abstract