Epilepsy Research Review™

Making Education Easy

Issue 13 - 2023

In this issue:

Abbreviations used in this issue:

CBD = cannabidiol; **EEG** = electroencephalography; **REM** = rapid eye movement; **RR** = risk ratio.

Welcome to the thirteenth issue of Epilepsy Research Review.

We begin this issue with three papers reporting on the use of CBD (cannabidiol) in epilepsy, the first of which is a meta-analysis focussing on safety, with the others also providing long-term, real-world data. These are followed by an investigation into the association of antiepileptic drugs and incident Parkinson's disease. The safety of antiseizure drug use as monotherapy during pregnancy in terms of major congenital malformations has also been evaluated. This issue concludes with important research describing shortages of antiseizure drugs in Australia, particularly generic brands.

Your comments and feedback are appreciated, so please keep sending them.

Kind Regards,

Professor Mark Cook AO
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Adverse events of cannabidiol use in patients with epilepsy

Authors: Fazlollahi A et al.

Summary: This was a systematic review and meta-analysis of data from nine studies reporting on adverse events in patients using CBD for epilepsy; three studies had raised concerns regarding bias, and three were at high risk of bias, prompting the authors to advise caution in interpreting the following results. Any grade adverse events occurred at a higher incidence among CBD recipients than study participants from control groups (9.7% vs. 4.0% RR 1.12 [95% CI 1.02–1.23]), with higher risks for severe-grade adverse events (RR 3.39 [1.42–8.09]), serious adverse events (2.67 [1.83–3.88]), adverse events leading to CBD discontinuation (3.95 [1.86–8.37]) and those resulting in a dose reduction (9.87 [5.34–14.40]).

Comment: The 'natural' origin of cannabinoids makes many patients presume that these agents are completely free of side effects. It's widely known that recreational cannabis use has other potential adverse health effects, but there has been emphasis on the low risk of CBD in its various preparations. This meta-analysis looks at the risks of significant adverse events across a range of circumstances and doses. The authors found quite a high rate of adverse effects, with a relative risk for severe grade adverse events of 3.39. These covered complaints such as diarrhoea, decreased appetite, disturbed liver function tests and pyrexia. Somnolence was also a significant problem. I think this paper provides some useful additional information with which to counsel patients when they are considering use of CBD preparations, so that the relative benefits can be put in perspective when compared with conventional therapies.

Reference: JAMA Netw Open 2023;6:e239126
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.

Long-term efficacy and safety of cannabidiol in patients with treatment-resistant epilepsies

Authors: Szaflarski JP et al.

Summary: These researchers reported 4-year outcomes for 892 patients (median age 11.8 years) with treatment-resistant epilepsy receiving Epidiolex® (a plant-derived highly purified CBD) 100 mg/mL oral solution for a median of 694 days as part of an expanded access programme, with the dosage increasing from 2 to 10 mg/kg/day to tolerance up to a maximum of 25–50 mg/kg/day depending on the study site. The patients were taking a median of three antiseizure medications at baseline, mostly clobazam, levetiracetam or valproate. Withdrawal due to lack of efficacy was reported by 19% of the patients, and withdrawal due to adverse events was reported by 7%. Median percentage reductions from baseline for convulsive and total seizures were 50–67% and 46–66%, respectively, with respective convulsive seizure rates for ≥50%, ≥75% and 100% reductions of 51–59%, 33–42% and 11–17%. The incidence of adverse events was 88% overall, with the most common being diarrhoea (33%), seizure (24%) and somnolence (23%), and the incidence of serious adverse events was 41%. None of the 20 deaths during the study were considered to be treatment-related.

Comment: This study continues the analysis of patients included in the CBD access programme in the USA, previously reported up to 2016, and here for subsequent years. As the study above noted, adverse events were quite common with adverse events reported in 88% of patients and serious in 41%. There was an 8% incidence of withdrawal through adverse events in this group, with 36% of subjects withdrawing over the study altogether. These were still younger patients, with a median age of about 12 years. Nearly half of them were taking clobazam. The percentage seizure reduction rates were about the same for convulsive seizures and seizures overall. Once again, the study demonstrates the efficacy of the agent, but confirms also use is not always free of problems, with a very significant proportion of side effects, not too dissimilar from other antiseizure drugs.

Reference: Epilepsia 2023;64:619–29
Abstract

Real-world, long-term evaluation of the tolerability and therapy retention of Epidiolex® (cannabidiol) in patients with refractory epilepsy

Authors: Georgieva D et al.

Summary: This retrospective review reported on 108 evaluable patients (mean age 20.3 years) with refractory epilepsy from a single centre who used Epidiolex® at a mean initial dosage of 5.3 mg/kg/day and a mean maintenance dosage of 15.3 mg/kg/day; three quarters of the patients were still receiving the CBD product at their final evaluation. Treatment-emergent adverse events were reported by 46.3% of the patients, and 14.5% discontinued due to such events; other reasons for discontinuation were lack of efficacy (37%), increased seizure activity (22%), worsened behaviour (22%) and sedation (22%), and there was one discontinuation due to liver function test perturbation. Of patients on concomitant clobazam at CBD initiation (47.2% of the patients), 39.2% decreased their dose of the former. Just over half the patients (53%) discontinued or lowered their dose of ≥1 other antiseizure medication.

Comment: This is a real-world but retrospective study of patients taking CBD for a range of epilepsies, with 108 subjects included here. The authors note that 75% of the patients remained on the agent, and that almost half of them experienced at least one treatment-emergent adverse effect, 14% of them discontinuing the drug because of that. Lack of efficacy, increase seizure activity, sedation and behavioural change as with all of the reports were the major reasons. The authors note that exploring ways to mitigate these adverse effects and also anticipate drug interactions (particularly with clobazam) may be important to consider in future use. As with all these three studies, there is no question of the utility in a significant number of patients, but recognition this may not be the best therapy for all patients, and tempers the early and sometimes uncritical claims made for CBD.

Reference: Epilepsy Behav 2023;141:109159
Abstract

Association between antiepileptic drugs and incident Parkinson disease

Authors: Belete D et al.

Summary: These researchers explored the association between antiepileptic drug use and incident Parkinson's disease in a nested case-control study of UK Biobank enrolees; cases were 1433 patients with Parkinson's disease, each matched to six controls. A significant association was detected between any antiepileptic drug prescription and incident Parkinson's disease (odds ratio 1.80 [95% CI 1.35–2.40]), with a trend for more prescriptions and multiple antiepileptic drug use being associated with a greater Parkinson's disease risk.

Comment: I was a bit apprehensive about including this abstract in the list, as we already have enough uncertainty about long-term side effects across an ever-increasing range of neurological and non-neurological consequences of antiseizure drug use. Nevertheless, it's the sort of information that often gets out into patient groups, and the media, so I think it's worth bringing to everyone's attention. Parkinsonism is certainly recognised as a complication of valproate use; probably less known is that it has been reported significantly associated with gabapentin and pregabalin. Very rarely lamotrigine has been implicated, but not levetiracetam. The study is well conducted, using the UK Biobank data. I think we would have to regard these as very interesting but still very preliminary observations. Similar observations were made against the use of the same range of agents in a German study based in primary care practices that was also published recently (Brain Sci 2023;13:450). This is certainly an area to watch.

Reference: JAMA Neurol 2023;80:183–7
Abstract

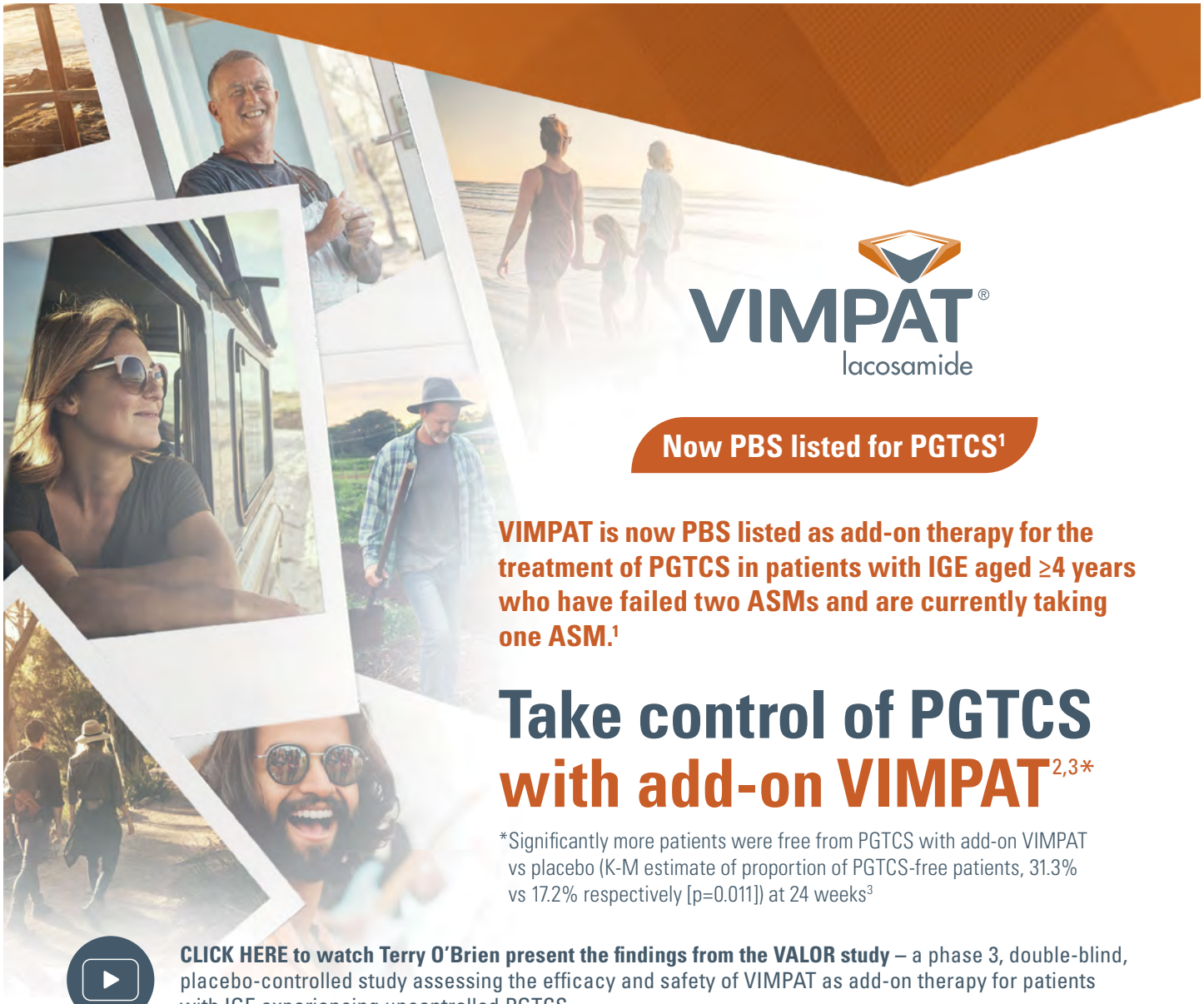
Genetic testing to inform epilepsy treatment management from an international study of clinical practice

Authors: McKnight D et al., and the ELEVIATE Consortium

Summary: Associations of genetic diagnoses with clinical management and outcomes were explored in this retrospective cross-sectional study of 418 patients with epilepsy (median age 4 years), with case report forms completed in a mean 595 days after the genetic tests were ordered. Changes in clinical management were made as a result of the genetic diagnosis for 49.8% of the patients; these changes were made within 3 months in 81.7% of the patients, and included adding a new medication in 21.7%, the initiation of medication in 14.2%, referral to a specialist in 13.4%, increased vigilance for subclinical or extraneurological disease features in 12.8%, and medication cessation in 11.7%. Among patients for whom follow-up clinical information was available (n=167), positive outcomes were recorded for 74.9%, seizure reduction or elimination was achieved in 64.7%, the severity of other clinical signs decreased in 22.2%, and reduced adverse effects to medications were seen in 6.6%. Worsening of outcomes included a decline in condition in 12.0%, increased seizure frequency in 3.6%, and adverse effects to medications in 1.8%. There were no clinical management changes recorded for 42.6% of the patients.

Comment: There have been such tremendous advances in understanding the genetics of epilepsy, but out in clinical practice, it isn't always clear that these discoveries have impacted management a great deal. This study looked at a large group of patience, sent for multigene panel testing to a commercial organisation, and it's important to note that the lead authors are employed by that organisation. Nevertheless, it's a large multicentre study spanning multiple academic centres. They found that a definite genetic diagnosis led to a change in clinical management for about 50% of patients, which is obviously quite a significant proportion. It's important to note though that the mean age of the 418 patients included was 4 years, although they did range up to 52 years. It's obvious the management implications of these genetic studies are far greater in a younger age group, but it does show that some headway is being made in translating genetic insights into clinical practice, with great benefit for patients and families.

Reference: JAMA Neurol 2022;79:1267–76
Abstract



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Now PBS listed for PGTCS[1]

VIMPAT is now PBS listed as add-on therapy for the treatment of PGTCS in patients with IGE aged ≥4 years who have failed two ASMs and are currently taking one ASM.[1]

Take control of PGTCS with add-on VIMPAT[2,3]*

*Significantly more patients were free from PGTCS with add-on VIMPAT vs placebo (K-M estimate of proportion of PGTCS-free patients, 31.3% vs 17.2% respectively [p=0.011]) at 24 weeks[3]

CLICK HERE to watch Terry O'Brien present the findings from the VALOR study – a phase 3, double-blind, placebo-controlled study assessing the efficacy and safety of VIMPAT as add-on therapy for patients with IGE experiencing uncontrolled PGTCS.

PBS INFORMATION: Partial seizures and primary generalised tonic-clonic seizures.
Tablets and Oral solution: Authority Required (STREAMLINED). Refer to the PBS schedule for full authority information. **Injection:** This product is not listed on the PBS.

Please review the full Product Information before prescribing.
The Product Information can be accessed at
www.ucbpharma.com.au/Vimpat-oral | www.ucbpharma.com.au/Vimpat-IV

Abbreviations: ASM, anti-seizure medication; **IGE,** idiopathic generalised epilepsy; **K-M,** Kaplan-Meier; **PGTCS,** primary generalised tonic-clonic seizure.

References: 1. PBS indication: https://www.pbs.gov.au/pbs/search?term=lacosamide. **2.** VIMPAT® Australian Approved Product Information. **3.** Vossler *DG et al. J Neurol Neurosurg Psychiatry* 2020; 91(10):1067–1075.

A subpopulation of spikes predicts successful epilepsy surgery outcome

Authors: Thomas J et al.

Summary: These researchers examined the potential for identifying specific spike features on intracranial EEG for optimal identification of the epileptogenic zone. They analysed spike features on stereo EEG segments from 83 operated patients during wakefulness, non-REM sleep and REM sleep, and then investigated the 135 spike features according to rate, morphology, propagation and energy to discriminate the epileptogenic zone in seizure-free and non-seizure-free patients. Compared with the current gold standard of seizure onset zone and with ripple rate (an emerging seizure-independent biomarker), the spike rate preceding gamma activity in wakefulness performed better for classifying surgical outcome (four-fold area under the curve 0.755 vs. 0.563 and 0.537, respectively [p values 0.0145 and 0.006]). There was an 80% probability that channels with a spike gamma rate >1.9 per min were in the epileptogenic zone. The results were not improved when features were combined.

Comment: There hasn't been an enormous amount of interest in recent years around the utility of spikes as a localiser for resection of the epileptogenic zone, although finding bilateral spikes in patients having epilepsy surgery is well known to be a negative predictor of surgical outcomes. This study is at another level of sophistication altogether, examining the relationship between spikes and invasive recording, correlating with surgical outcomes across a broad range of pathologies. This careful study examined findings from stereo EEG, identifying a subpopulation of spikes (spike gamma) amongst patients, and found that this was the single best feature for predicting a favourable surgical outcome, better even than seizure onset zone and ripple rate estimations. The fact that these estimations can be made without necessarily requiring seizure capture makes it potentially a very attractive addition to the current suite of analytical tools in surgical planning. As with much work of this type, it will be interesting to see if it can be replicated at other centres.

Reference: Ann Neurol 2023;93:522–35
Abstract

Neuropathological insights into unexpected cognitive decline in epilepsy

Authors: Reimers A et al.

Summary: In-depth neuropathological examinations were undertaken of resected specimens from patients who unexpectedly displayed an unfavourable cognitive course after epilepsy surgery subsequent to any direct cognitive sequelae of the surgery, with the aim of exploring underlying disease processes; matched patients without cognitive deterioration served as controls. Of 355 operated patients who had undergone >1 postoperative neuropsychological examination, 30 exhibited significant cognitive decline postsurgery, and of 24 with available specimens, 71% displayed further neuropathological changes beyond the typical spectrum. These additional changes indicated: i) a secondary, putatively epilepsy-independent neurodegenerative disease process; ii) limbic inflammation; or iii) an enigmatic pathology pattern of 'hippocampal gliosis' in the absence of segmental neurodegeneration. Matched individual principal epilepsy-associated pathologies among controls were not seen in combination with any of the secondary pathology patterns identified in the study group.

Comment: Unexpected postoperative decline in cognitive function after epilepsy surgery that isn't explained by the extent or site of surgical resection is an uncommon but challenging problem in this area. This study examined the pathological findings in a group of such patients, finding over two-thirds had neuropathological changes in addition to those related directly to the aetiology of their seizures, which the authors presumed reflect independent neurodegenerative disease processes. Some had limbic inflammation or other less well clarified alternative pathologies. This spectrum of changes was not found in a matched control group. These are interesting findings and potentially very important in terms of understanding how best to assess and manage patients who fall into this group. It is quite a small study though, with only 24 patients having available specimens, and so further work is required as the authors propose, and certainly this is something that would be well suited to a multicentre approach as they propose.

Reference: Ann Neurol 2023;93:536–50
Abstract

Comparative safety of antiseizure medication monotherapy for major malformations

Authors: Cohen JM et al.

Summary: Risks of major congenital malformations associated with antiseizure medication monotherapy use during pregnancy were explored in a population-based Scandinavian cohort. Compared with 4,866,362 pregnancies without antiseizure medication exposure, those with lamotrigine monotherapy exposure (n=8339) were associated with a higher crude risk of any major congenital malformation, but significance of the association was lost after adjusting for confounders (adjusted RR 0.97 [95% CI 0.87–1.08]). However, compared with lamotrigine, the risk of malformations was significantly increased by use of valproate (n=2031) and of topiramate (n=509) during pregnancy (respective adjusted RRs 2.05 [95% CI 1.70–2.46] and 1.81 [1.26–2.60]), with the risk increasing as the dose increased, but not by use of carbamazepine (n=2674), oxcarbazepine (n=1313) or levetiracetam (n=1040). Malformation subtypes associated with valproate use during pregnancy included nervous system, cardiac, oral clefts, clubfoot and hypospadias; no subtypes associated with lamotrigine or carbamazepine were identified.

Comment: It's pleasing to see so many publications, now looking at studies of very large groups of patients, to try and identify more precisely the risks associated with antiseizure drugs and major congenital malformations. This study of over 8000 patients compared lamotrigine against valproate, topiramate, carbamazepine, oxcarbazepine and levetiracetam and found, as expected, that valproate was associated with the highest rate of major congenital malformations, but also that topiramate had a similar risk. As with valproate, the lower doses of topiramate seemed to mitigate the risk. No increase risk was found with lamotrigine, carbamazepine, oxcarbazepine or levetiracetam. Once again, this is useful information to have available in the clinic when discussing the risk of these drugs with patients.

Reference: Ann Neurol 2023;93:551–62
Abstract

A phase 1 open-label trial evaluating focused ultrasound unilateral anterior thalamotomy for focal onset epilepsy

Authors: Krishna V et al.

Summary: Two adults with treatment-refractory, focal-onset epilepsy received focused ultrasound ablation to the anterior nucleus of the thalamus in this pilot study. Both participants tolerated the procedure with no neurological deficits or serious adverse events developing. Declines in verbal fluency, attention/working memory and immediate verbal memory occurred in one of the participants, but both experienced significant reductions in seizure frequency, with one achieving freedom from seizures at 12 months and the other achieving a reduction in their seizure frequency from 90–100 to 3–6 seizures per month.

Comment: This is a very small study obviously, with only two patients, but showing positive results with the application of focused ultrasound in refractory focal epilepsy. Because of the increasing availability and experience of these MR-guided systems for the treatment of Parkinson's disease, there will no doubt be a lot of interest in the potential opportunities provided by this therapy, particularly as it is noninvasive and relatively safe. It's an evolving area though, and there are still many uncertainties. Nevertheless, this very small but careful analysis shows very impressive results, and certainly warrants further exploration.

Reference: Epilepsia 2023;64:831–42
Abstract

Shortages of antiseizure medications in Australia and the association with patient switching, and adherence in a community setting

Authors: Welton J et al.

Summary: These authors reported on sponsor-reported oral antiseizure medication shortages in Australia and their impacts on patients. During the 2019–2020 period, there were 97 sponsor-reported antiseizure medication shortages, 93% of which were for generic brands, and 19.5% of the >1 million patients dispensed ≥1 antiseizure medication were impacted. Although the frequency of sponsor-reported shortages was greater prior to the COVID-19 pandemic than during the pandemic, it was estimated that more patients were impacted during the pandemic than before it. There were an estimated 330,872 patient-level shortage events recorded, with shortages of generic brands accounting for 98.5%. The rate of shortages of generic brands was substantially greater than for originator brands (41.06 vs. 0.83 shortages per 100 person-years). Around two-thirds of patients on a levetiracetam formulation affected by a shortage were switched to a different brand or formulation of the drug, compared with 46.6% during periods when there were no shortages.

Comment: This important study looked at an area that is probably inadequately considered in clinical practice, although the consistent supply of drugs has been a recurring problem over the years, and it is interesting that this has become more of an issue as the number of generic drugs has increased. It's interesting also that sponsor-reported shortages seem to have been more frequent before COVID-19, although the authors consider that more patients were actually affected by shortages during the pandemic, and this would reflect clinical experience. Complexities around manufacturing, logistics and pharmacy supply arrangements represent a significant and inadequately considered problem for the management of epilepsy in Australia, and no doubt similar values will be found in international scenarios. When the consequences are potentially so significant, this is a matter that deserves more attention.

Reference: Epilepsy Behav 2023;141:109145
Abstract