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Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy.

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OBJECTIVE: To examine long-term retention rate, clinical outcomes, cost-utility and cost-effectiveness of the Ketogenic Diet (KD) compared with care as usual (CAU) in children and adolescents with intractable epilepsy from a societal perspective.

METHODS: Participants were randomized into a KD or CAU group. Seizure frequency, quality adjusted life years (QALYs), side-effects, seizure severity, health care costs, production losses, patient and family costs were assessed at baseline and during 16-months of follow-up. Incremental cost-effectiveness ratios (ICERs) (i.e. cost per QALY and cost per responder) and cost-effectiveness acceptability curves are presented.

RESULTS: 48 children were included in the analyses of this study (26 from KD group). In total, 58% of the KD group completed the follow-up of 16 months; 11 dropped-out for various reasons. At 16 months, 35% of the KD participants had a seizure reduction $\geq 50\%$ from baseline, compared with 18% of the CAU participants. Mean costs per patient in the CAU group were €53,367 (extrapolated) compared to

€61,019 per patient in the KD group, resulting in an ICER of €46,564 per responder. Cost per QALY rose well above any acceptable ceiling ratio. At 4-months' follow-up, the KD group showed significantly more gastro-intestinal problems compared to the CAU group. At 16 months, the KD group reported fewer problems compared to CAU. Furthermore, 46.2% of the KD group reported a decrease in severity of their worst seizure compared to 32% of the CAU group.

CONCLUSION: The KD group resulted in more responders and showed greater improvement on seizure severity. Furthermore, the KD did not lead to worsening of side-effects other than gastro-intestinal problems (only at 4 months' follow-up). However, as only a minimal difference in QALYs was found between the KD group and the CAU group, the resulting cost per QALY ratios were inconclusive.

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Panic symptoms in transient loss of consciousness: Frequency and diagnostic value in psychogenic nonepileptic seizures, epilepsy and syncope.

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PURPOSE: Previous studies suggest that ictal panic symptoms are common in patients with psychogenic nonepileptic seizures (PNES). This study investigates the frequency of panic symptoms in PNES and if panic symptoms, just before or during episodes, can help distinguish PNES from the other common causes of transient loss of consciousness (TLOC), syncope and epilepsy.

METHODS: Patients with secure diagnoses of PNES (n=98), epilepsy (n=95) and syncope (n=100) were identified using clinical databases from three United Kingdom hospitals. Patients self-reported the frequency with which they experienced seven symptoms of panic disorder in association with their episodes. A composite panic symptom score was calculated on the basis of the frequency of symptoms.

RESULTS: 8.2% of patients with PNES reported "never" experiencing any of the seven panic symptoms in their episodes of TLOC. Patients with PNES reported more frequent panic symptoms in their attacks than those with epilepsy ($p<0.001$) or syncope ($p<0.001$), however, patients with PNES were more likely "rarely" or "never" to report five of the seven-ictal panic symptoms than "frequently" or "always" (45-69% versus 13-29%). A receiver operating characteristic analysis demonstrated that the composite panic symptom score distinguished patients with PNES from the other groups (sensitivity 71.1%, specificity 71.2%), but not epilepsy from syncope.

CONCLUSIONS: Patients with PNES report TLOC associated panic symptoms more commonly than those with epilepsy or syncope. Although panic symptoms are reported infrequently by most patients with PNES, a composite symptom score may contribute to the differentiation between PNES and the other two common causes of TLOC.

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Effects of antiepileptic drugs on thyroid hormone function in epilepsy patients.

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PURPOSE: Patients with epilepsy are frequently required to take antiepileptic drugs (AEDs) for a long period of time. Many studies have shown that AEDs have a negative influence on endocrine function including the thyroid gland, however the risk factors for the development of low thyroid function in these patients are unclear. This study aimed to determine the potential risk factors of low thyroid function in patients with epilepsy.

METHOD: This was a cross-sectional study including 298 patients with epilepsy. Patients with previous thyroid disease were excluded. Epidemiologic data, type of epilepsy, etiology, the age of seizure onset, duration of epilepsy, intractable epilepsy, and number and dosage of AEDs were recorded. Levels of free thyroxine (fT4) and thyroid stimulating hormone (TSH) were measured.

RESULTS: Fifty-two of the 298 (17.4%) patients had low fT4. Older age ($P=0.004$), female sex ($P=0.014$), longer duration of epilepsy ($P=0.001$), and intractable epilepsy ($P=0.009$) were significantly associated with low fT4. Regarding individual AEDs, carbamazepine (30.1%), topiramate (28.6%), and levetiracetam (24.3%) were significantly associated with the presence of low fT4. After stepwise logistic regression of all significant variables, female sex, older age, three or more AEDs, and carbamazepine were independent risk factors for low fT4.

CONCLUSIONS: Female patients with epilepsy and an older age, AED polytherapy, and carbamazepine treatment had a higher risk of low fT4. Thyroid function in these patients should be monitored closely.

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Real-life experience with brivaracetam in 101 patients with difficult-to-treat epilepsy-A monocenter survey.

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PURPOSE: To assess the efficiency of brivaracetam under real-world conditions in a tertiary referral epilepsy center.

METHODS: We consecutively collected patients treated at our center with brivaracetam (BRV). After a minimum observation period of six months we retrospectively analyzed the efficiency of BRV.

RESULTS: Data of 101 patients (mean age 42 years, range 18-81 years, 54 females,) were analyzed. The median number of antiepileptic drugs (AEDs) used prior to BRV was 10 (range 2-18). The initial dose of BRV was at least 50mg per day, the mean maintenance dose at cut-off was 168.6mg (median 200mg, range 50-400mg). Efficacy data were assessed for the last three months or at the time of the last observation carried forward if BRV had been discontinued prematurely. Responder rate was 27.8% ($n=28$) with 7% seizure-free patients. Adverse events (AEs) occurred in 37 patients (37%). Most frequent AEs were dizziness (16%) and somnolence (11%). Psychiatric adverse events comprised irritability, aggression, depression and psychosis in single cases. Retention rate after six months was 51.5%. Main reason for discontinuation was a lack of efficacy. In 43 cases LEV and BRV were switched. The switch was performed abruptly without complications. In 26 cases (60%) BRV was discontinued and re-switched to LEV within weeks, mainly due to a lack of better efficacy. After the switch from LEV to BRV we even saw an aggravation both of seizure frequency and severity in 5 cases. Retention rate in patients who had not been on LEV was 57%.

CONCLUSION: In our hands BRV appeared to be well tolerated and easy to handle. The retention rate was influenced by patients who were switched from LEV and re-switched because BRV was not more efficient. Switching from and re-switching to LEV was easy.

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Absence epilepsy beyond adolescence: an outcome analysis after 45 years of follow-up.

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OBJECTIVES: Depending on patient age at onset, absence epilepsy is subdivided into childhood and juvenile forms. Absence seizures can occur several times per day (pyknoleptic course) or less frequently than daily (non-pyknoleptic course). Seizures typically terminate before adulthood, but a quarter of patients need ongoing treatment beyond adolescence. Little is known about their long-term seizure and psychosocial outcome.

METHODS: Files of 135 outpatients with absence epilepsy (76 females; 123 had additional generalised tonic-clonic seizures) were retrospectively analysed after a median follow-up of 45.4 years (IQR: 31.9-56.2). Eighty-two subjects completed an additional interview. Patients were dichotomised according to age at epilepsy onset (childhood: n=82; juvenile: n=53) and course of absence seizures (pyknoleptic: n=80; non-pyknoleptic: n=55).

RESULTS: Among all patients, 53% achieved 5-year terminal seizure remission, 16% without antiepileptic medication. Median age at last seizure was lower in patients with childhood onset of absence epilepsy (37.7 years) versus juvenile onset (44.4 years; $P \leq 0.01$). However, rates and duration of terminal seizure remission were similar. Pyknoleptic versus non-pyknoleptic course of absence seizures made no difference for long-term seizure outcome. Multivariate analysis identified only higher age at investigation to be associated with terminal 5-year seizure remission. Regarding aspects of psychosocial outcome, there were no significant differences between the respective subgroups.

CONCLUSIONS: These data indicate that if absence epilepsy persists beyond adolescence, long-term seizure and psychosocial outcome do not differ between childhood and juvenile onset or between pyknoleptic and non-pyknoleptic course of absence epilepsy. However, higher patient age increases the chance of terminal seizure remission.

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The association between dementia and epilepsy: A systematic review and meta-analysis.

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OBJECTIVE: Dementia is among the top 15 conditions with the most substantial increase in burden of disease in the past decade, and along with epilepsy, among the top 25 causes of years lived with disability worldwide. The epidemiology of dementia in persons with epilepsy, and vice versa, is not well characterized. The purpose of this systematic review was to examine the prevalence, incidence, and reported risk factors for dementia in epilepsy and epilepsy in dementia.

METHODS: Embase, PsycINFO, MEDLINE, and the Cochrane databases were searched from inception. Papers were included if they reported the incidence and/or prevalence of dementia and epilepsy. Two individuals independently performed duplicate abstract and full-text review, data extraction, and quality assessment.

Random-effects models were used to generate pooled estimates when feasible.

RESULTS: Of the 3,043 citations identified, 64 were reviewed in full text and 19 articles were included. The period prevalence of dementia ranged from 8.1 to 17.5 per 100 persons among persons with epilepsy (insufficient data to pool). The pooled period prevalence of epilepsy among persons with dementia was 5 per 100 persons (95% confidence interval [CI] 1-9) in population-based settings and 4 per 100 persons (95% CI 1-6) in clinic settings. There were insufficient data to report a pooled overall incidence rate and only limited data on risk factors.

SIGNIFICANCE: There are significant gaps in knowledge regarding the epidemiology of epilepsy in dementia and vice versa. Accurate estimates are needed to inform public health policy and prevention, and to understand health resource needs for these populations.

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Personality traits of children before and after epilepsy surgery.

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We studied how children with epilepsy (CWE) who are candidates for epilepsy surgery, perceive themselves with respect to overarching personality traits and whether the traits change after surgery. We explored influences of demographic and illness variables. A total of 23 CWE [mean age at inclusion 12.8 (sd 2.3); 12 girls] participated. Using the Dutch Personality Questionnaire Juniors (DPQ-J), we assessed 20 of the CWE shortly before epilepsy surgery and compared the results to those of 39 age- and gender-matched healthy controls. Furthermore, we obtained follow-up scores 6, 12 and 24 months after epilepsy surgery from the clinical group. CWE who were candidates for epilepsy surgery scored above average in inadequacy, perseverance, social inadequacy and recalcitrance, whereas healthy peers scored average. Over the two years' period after epilepsy surgery we found no changes, apart from a decrease of social inadequacy. Sporadic illness and demographic variables were related to some personality traits. However, neither post-surgical seizure freedom nor cessation of AEDs did noticeably change the self-evaluations of CWE. Asking CWE to evaluate their personality themselves may offer a shared basis for individually tailored behavior intervention in order to help them adapting to their ameliorated circumstances after surgery.

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Incidence of seizures following initial ischemic stroke in a community-based cohort: The Framingham Heart Study.

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PURPOSE: We examined the incidence of seizures following ischemic stroke in a community-based sample.

METHODS: All subjects with incident ischemic strokes in the Framingham Original and Offspring cohorts between 1982 and 2003 were identified and followed for up to 20 years to determine incidence of seizures. Seizure-type was based on the 2010 International League Against Epilepsy (ILAE) classification. Disability was stratified into mild/none, moderate and severe, based on post-stroke neurological deficit documentation according to the Framingham Heart Study (FHS) protocol and functional status was determined using the Barthel Index.

RESULTS: An initial ischemic stroke occurred in 469 subjects in the cohort and seizures occurred in 25 (5.3%) of these subjects. Seizure incidence was similar in both large artery atherosclerosis (LAA) (6.8%) and cardio-embolic (CE) (6.2%) strokes. No seizures occurred following lacunar strokes. The predominant seizure type was focal seizure with or without evolution to bilateral convulsive seizure. One third of participants had seizures within the first 24h from stroke onset and half of all seizures occurred within the first 30days. On multivariate analysis, moderate and severe disability following stroke was associated with increased risk of incident seizure.

CONCLUSIONS: Seizures occurred in approximately 5% of subjects after an ischemic stroke. One third of these seizures occurred in the first 24h after stroke and none followed lacunar strokes. Focal seizures with or without evolution in bilateral convulsive seizures were the most common seizure type. Moderate and severe disability was predictive of incident seizures.

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Eslicarbazepine acetate: its effectiveness as adjunctive therapy in clinical trials and open studies.

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Eslicarbazepine acetate (ESL) is a once-daily antiepileptic drug that is approved as adjunctive therapy in adults with focal-onset seizures. Following oral administration, ESL is rapidly metabolized to its active metabolite, eslicarbazepine, which acts primarily by enhancing slow inactivation of voltage-gated sodium channels. The efficacy and safety/tolerability of ESL in the adjunctive setting were established in a comprehensive Phase III program (n = 1702 randomized patients) and this evidence has been supported by several open studies (n = 864). ESL treatment has demonstrated improvements in health-related quality of life, in both randomized clinical trials and open studies. ESL has also been shown to be usually well tolerated and efficacious when used in the adjunctive setting in elderly patients. The effectiveness of ESL as the only add-on to antiepileptic drug monotherapy has been demonstrated in a multinational study (n = 219), subgroup analyses of which have also shown it to be efficacious and generally well tolerated in patients who had previously not responded to carbamazepine therapy. Open studies have also demonstrated improvements in tolerability in patients switched overnight from oxcarbazepine to ESL. Due to differences in pharmacokinetics, pharmacodynamics, and metabolism, there may be clinical situations in which it is appropriate to consider switching patients from oxcarbazepine or carbamazepine to ESL.

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Steps to prevent SUDEP: the validity of risk factors in the SUDEP and seizure safety checklist: a case control study.

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Our objectives were to compare people with epilepsy (PWE) who died of sudden unexpected death in epilepsy (SUDEP) with live controls using the risk factor items of the SUDEP and Seizure Safety Checklist. All 48 SUDEPs of 93 epilepsy deaths which occurred in Cornwall UK 2004-2012 were compared to 220 live controls using the SUDEP and Seizure Safety Checklist, an evidenced based tool used to communicate person centered risk of SUDEP to PWE. The odds ratio for having a specific factor in those who died was compared to controls and ranked according to P value using a sequential Bonferroni correction for multiple comparisons. Of the 17 modifiable and non-modifiable risk factors analyzed 9 were statistically

significant of which 7 are potentially modifiable. Well known modifiable factors such as nocturnal monitoring, compliance and sleeping position featured prominently in the risk association. This is the first case control study exploring the risk factors for SUDEP since 2009. The findings are compared to the current considered risk factors as identified in a major recent review. The study further validates certain SUDEP risk factors. It highlights that the majority of risk factors strongly associated with SUDEP are potentially modifiable. There is an emerging profile to rank the risk factors. It furthers the evidence to use structured risk assessment and communication tools such as the SUDEP and Seizure Safety Checklist in daily clinical practice. It highlights key areas for a person centered discussion to empower PWE to mitigate risk.

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Seizure Outcomes in Occipital Lobe and Posterior Quadrant Epilepsy Surgery: A Systematic Review and Meta-Analysis.

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BACKGROUND: Occipital lobe epilepsy (OLE) is an uncommon but debilitating focal epilepsy syndrome with seizures often refractory to medical management. While surgical resection has proven a viable treatment, previous studies examining postoperative seizure freedom rates are limited by small sample size and patient heterogeneity, thus exhibiting significant variability in their results.

OBJECTIVE: To review the medical literature on OLE so as to investigate rates and predictors of both seizure freedom and visual outcomes following surgery.

METHODS: We reviewed manuscripts exploring surgical resection for drug-resistant OLE published between January 1990 and June 2015 on PubMed. Seizure freedom rates were analyzed and potential predictors were evaluated with separate meta-analyses. Postoperative visual outcomes were also examined.

RESULTS: We identified 27 case series comprising 584 patients with greater than 1 yr of follow-up. Postoperative seizure freedom (Engel class I outcome) was observed in 65% of patients, and was significantly predicted by age less than 18 yr (odds ratio [OR] 1.54, 95% confidence interval [CI] 1.13-2.18), focal lesion on pathological analysis (OR 2.08, 95% CI 1.58-2.89), and abnormal preoperative magnetic resonance imaging (OR 3.24, 95% 2.03-6.55). Of these patients, 175 also had visual outcomes reported with 57% demonstrating some degree of visual decline following surgery. We did not find any relationship between postoperative visual and seizure outcomes.

CONCLUSION: Surgical resection for OLE is associated with favorable outcomes with nearly two-thirds of patients achieving postoperative seizure freedom. However, patients must be counseled regarding the risk of visual decline following surgery.

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Video ambulatory EEG: A good alternative to inpatient video telemetry?

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PURPOSE: Video ambulatory EEG (V-AEEG) is a new technique which could add increased capacity for long term EEG monitoring to overstretched inpatient video telemetry (IPVT) services. We compare V-AEEG and IPVT for diagnostic efficacy, recording quality, patient acceptability and technologist time required.

METHODS: Forty-one V-AEEG and 64 IPVT adult patients were included. Patients were investigated to diagnose attacks or to obtain polysomnography (PSG) prior to multiple sleep latency test (MSLT). Number of attacks recorded, whether the diagnostic question was answered, quality of video and EEG recording and patients' preference for investigation at home or in hospital were noted. For V-AEEG patients, ease of procedure and extra technologist time required were recorded.

RESULTS: Of patients investigated for diagnosis of attacks, 74% V-AEEG patients and 62% IPVT had typical attacks during the investigation. All PSGs were useful in interpreting the MSLTs. Diagnostic questions were answered by 73% V-AEEGs and 73% IPVTs. Quality of EEG and video recording was similar using V-AEEG and IPVT. Four patients had difficulty using V-AEEG equipment but diagnostic information was lost in only one. 5% of V-AEEG patients would have preferred hospital investigation but 45% of IPVT patients would have preferred home investigation. Extra technologist time for home visits (mean 2h) was required only for the first 7 patients.

CONCLUSION: Video EEG recording quality and diagnostic efficacy from V-AEEG are similar to IPVT. V-AEEG is acceptable to most patients and does not require additional technical time. Hence, V-AEEG offers a convenient, economical alternative to IPVT.

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The role of postictal laboratory blood analyses in the diagnosis and prognosis of seizures.

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BACKGROUND: Epileptic seizures (ES) lead to alterations in the blood laboratory

values and reflect changes in different organ systems. Here, we review the diagnostic and prognostic value of various blood laboratory values within the context of epilepsy.

METHODS: Narrative review and literature search on PubMed using the term, "seizure" and various laboratory values.

RESULTS: Laboratory markers can help clinicians determine whether an unwitnessed event was more likely to be epileptic or non-epileptic. Prolactin testing helps differentiate ES from psychogenic non-epileptic seizures (PNES) in adults and adolescents, and is associated with high specificity and moderate sensitivity. Elevations in the creatine kinase (CK) levels are common after generalized tonic-clonic seizures (GTCS) and display high specificity and moderate sensitivity. Metabolic markers such as ammonia and lactate may have diagnostic potential for postictal blood tests. Analyzing blood postictally is important for identifying the cause of the symptomatic seizures due to endocrine, metabolic, toxic or infectious etiologies. Finally, laboratory analyses are used for identifying patients who are at risk for developing rare, threatening complications such as rhabdomyolysis, acute renal failure (ARF) or cardiomyopathy.

CONCLUSIONS: Presently, no postictal laboratory values can definitively prove or rule out the diagnosis of an epileptic seizure. For seizures with unknown causes, simple blood tests can be a valuable aid for quickly defining the etiology, particularly with certain metabolic and toxic encephalopathies. For this reason, CK, electrolytes, creatinine, liver and renal function tests should be measured on at least one occasion. Further research is needed in order to identify new biomarkers that improve the diagnosis and prognosis of seizures and seizure-related complications.

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Evaluating the single seizure clinic model: Findings from a Canadian Center.

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INTRODUCTION: The effect of the single seizure clinic (SSC) model on patient diagnose, work-up, wait-times, and clinical care is poorly characterized and its efficacy unclear. The present study assesses patient characteristics and evaluates the impact of a single seizure clinic (SSC) model on wait-times and access to care.

MATERIAL AND METHODS: A prospective study of all patients (n=200) referred to our SSC for first seizure evaluation. Demographic, clinical, and paraclinical variables were systematically collected and analyzed against a historical cohort.

Binary logistic regression analysis was performed to predict impact of dichotomized variables on diagnosis of epilepsy. Diagnostic concordance between SSC nurses and epileptologists was also assessed.

RESULTS: Predominant referral sources were emergency department physicians and general practitioners. Mean wait-time for first assessment was significantly reduced by 70.5% employing the SSC model versus historical usual care. A diagnosis was established at first-contact in 80.5% of cases while 16.0% of patients required a second visit. Eighty-two patients (41.0%) were diagnosed with epilepsy. An abnormal EEG was found in 93.9% of patients diagnosed with epilepsy. Sixty-three patients were started on anti-epileptic drugs (63.5% lamotrigine, 7.0% levetiracetam, 5.0% phenytoin, and 5.0% topiramate). In 18% of cases driving restrictions were initiated by the SSC. The most common non-seizure diagnosis was syncope (24.0%).

DISCUSSION: The SSC reduced wait-times for assessment and investigations, clarified diagnoses, affected management decisions with respect to further workup, pharmacotherapy, and driving. There was moderate correlation between SSC nurses and physicians ($\kappa=0.54$; $p<0.001$) as physicians were significantly more likely to diagnose epilepsy. Key factors identified as predictors of epilepsy were: presence of abnormalities on electroencephalography and imaging studies, patients stratified as high or medium-risk for seizure recurrence, semiological characteristics such as amnesia and limb stiffening, and presence of tongue trauma, or incontinence.

CONCLUSIONS: The SSC model reduces wait-times, streamlines assessments, and impacts clinical care decisions.

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Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society.

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OBJECTIVE: To determine the incidence rates of sudden unexpected death in epilepsy (SUDEP) in different epilepsy populations and address the question of whether risk factors for SUDEP have been identified.

METHODS: Systematic review of evidence; modified Grading Recommendations Assessment, Development, and Evaluation process for developing conclusions; recommendations developed by consensus.

RESULTS: Findings for incidence rates based on 12 Class I studies include the following: SUDEP risk in children with epilepsy (aged 0-17 years) is 0.22/1,000 patient-years (95% confidence interval [CI] 0.16-0.31) (moderate confidence in evidence). SUDEP risk increases in adults to 1.2/1,000 patient-years (95% CI 0.64-2.32) (low confidence in evidence). The major risk factor for SUDEP is the occurrence of generalized tonic-clonic seizures (GTCS); the SUDEP risk increases in association with increasing frequency of GTCS occurrence (high confidence in evidence).

RECOMMENDATIONS: Level B: Clinicians caring for young children with epilepsy should inform parents/guardians that in 1 year, SUDEP typically affects 1 in 4,500 children; therefore, 4,499 of 4,500 children will not be affected.

Clinicians should inform adult patients with epilepsy that SUDEP typically affects 1 in 1,000 adults with epilepsy per year; therefore, annually 999 of 1,000 adults will not be affected. For persons with epilepsy who continue to experience GTCS, clinicians should continue to actively manage epilepsy therapies to reduce seizures and SUDEP risk while incorporating patient preferences and weighing the risks and benefits of any new approach. Clinicians should inform persons with epilepsy that seizure freedom, particularly freedom from GTCS, is strongly associated with decreased SUDEP risk.

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Efficacy of Treatments for Infantile Spasms: A Systematic Review.

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OBJECTIVES: West syndrome (also known as infantile spasm because of its main seizure type) is a rare form of epilepsy that begins during early infancy. Recent guidelines and reviews on West syndrome recommend the use of adrenocorticotropic hormone steroids, or vigabatrin, as the first-line treatment. However, West

syndrome remains to be one of the most challenging epilepsies to treat. Here, we systematically reviewed the current literature obtained during the previous decade. This article provides an overview of the current treatment of infantile spasms.

METHODS: PubMed and EMBASE were searched to retrieve studies on human published during 2005-2015 and to identify patients with clinical diagnosis of infantile spasms. Drug or diet treatments were used as interventions and comparators.

RESULTS: We included 55 studies, of which 1 study was a meta-analysis, 9 were randomized controlled trials, 21 were prospective studies, and 24 were retrospective studies. Topiramate, levetiracetam, zonisamide, and sodium valproate with benzodiazepine (clonazepam or nitrazepam) were found to be potential drugs for treating West syndrome besides adrenocorticotrophic hormone, steroids, and vigabatrin. Ketogenic diet and modified Atkins diet were also found to be effective.

CONCLUSIONS: To date, data regarding the efficacy of treatments of West syndrome still remain limited. Some treatments, including topiramate and ketogenic diet, seem promising besides adrenocorticotrophic hormone, steroids, and vigabatrin. Well-designed trials are warranted to validate the findings.

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Three-Year Retention Rates of Levetiracetam, Topiramate, and Oxcarbazepine: A Retrospective Hospital-Based Study.

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OBJECTIVES: We evaluated and compared the 3-year retention rates of levetiracetam (LEV), topiramate (TPM), and oxcarbazepine (OXC) in patients with epilepsy in routine clinical practice.

METHODS: We retrospectively reviewed medical records of patients with epilepsy who were newly prescribed LEV, TPM, or OXC from 2006 to 2010. The retention rates were estimated by the Kaplan-Meier analysis, and independent risk factors for drug discontinuation were analyzed by the Cox regression method.

RESULTS: A total of 588 patients were included: LEV (n = 345), TPM (n = 190), and OXC (n = 53). Among them, 82% had focal epilepsy, whereas 14.8% had generalized epilepsy. The 3-year retention rates for LEV, TPM, and OXC, were 81.2%, 78.3%, and 54.7%, respectively. Levetiracetam and TPM had equivalent retention rates, whereas patients remained on OXC for a significantly shorter amount of time (P < 0.001). A lower retention rate for OXC was also evident in the subgroup analysis of focal epilepsy (P < 0.001). In generalized epilepsy, LEV and TPM revealed comparable retention rates (P = 0.255). The seizure-freedom rate did not differ

among groups, whereas the rate of adverse effects leading to drug withdrawal of OXC (87.5%) was higher than that of LEV (34.4%, $P < 0.001$) and TPM (52.5%, $P = 0.012$).

CONCLUSIONS: The current study suggested that LEV and TPM had comparable retention profiles in the long-term treatment for both focal and generalized epilepsy. Meanwhile, OXC therapy seemed to be relatively less useful because of its poor tolerability.

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Anxiety and depressive disorders in people with epilepsy: A meta-analysis.

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OBJECTIVE: Comorbid anxiety and depressive disorders in people with epilepsy (PWE) are highly prevalent and associated with various adverse outcomes. However, the prevalence of anxiety disorders in PWE across studies is highly variable. Our aim was to estimate the prevalence and moderating factors of anxiety and depressive disorders in PWE.

METHODS: Following prospective registration (PROSPERO; CRD42015027101), electronic databases were searched for studies that reported the prevalence of both anxiety and depressive disorders in samples of PWE up until July 2016. Data extracted included the prevalence of anxiety and depressive disorders, and moderators of interest (e.g., method of diagnosis, prevalence of drug-resistant epilepsy). Meta-analysis of the overall pooled prevalence of anxiety and depressive disorders was conducted.

RESULTS: The search yielded 8,636 unique articles, with 27 studies meeting final inclusion criteria (3,221 PWE). The pooled prevalence of anxiety and depressive disorders was 20.2% (95% confidence interval [CI] 15.3-26.0%) and 22.9% (95% CI 18.2-28.4%), respectively. Method of diagnosis significantly moderated anxiety disorder prevalence (Q statistic with one degree of freedom [Q1] = 36.29, $p < 0.0001$); the prevalence of anxiety disorders based on unstructured clinician assessment was 8.1% (95% CI 5.7-11.4%), compared to a prevalence of 27.3% (95% CI 22.1-33.3%) based on a structured clinical interview. There were no significant moderators of depressive disorder diagnosis.

SIGNIFICANCE: Findings suggest the prevalence of anxiety and depressive disorders in PWE are equivalent, and variability in prevalence of anxiety disorders across studies can be attributed partly to the method of diagnosis. These findings also challenge widely held assumptions that psychiatric comorbidity is more common in people with drug-resistant epilepsy. Future research should aim to improve the detection and management of these comorbidities in PWE, particularly anxiety disorders, which have remained relatively neglected.

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Psychiatric and behavioral comorbidities in epilepsy: A critical reappraisal.

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Psychiatric and behavioral disorders are important aspects of epilepsy and have received increasing attention in the last several years. The literature upon which most of the field relies contains some biases that must be carefully examined and resolved in future studies. First, in the pediatric epilepsy literature, many reports find that children with epilepsy have high levels of behavioral and psychiatric disorders when compared to appropriate controls. Most of these studies rely on parent-proxy completed instruments to assess these behavioral endpoints. Parents' reports are not objective but reflect parents' reactions and emotions. Increasing evidence suggests inherent biases in proxy reports and highlights the need to assess children directly. Second, periictal phenomena may be mischaracterized as underlying mood disorders. Third, many studies report elevated levels of psychiatric morbidity before and after the diagnosis of epilepsy, suggesting an inherent relation between the two types of disorders. Psychogenic nonepileptic seizures, while widely recognized as posing a diagnostic dilemma in the clinic, may account for some of these research findings. Diagnostic errors between epilepsy and psychogenic nonepileptic seizures need careful consideration when evaluating studies demonstrating associations between psychiatric disorders and epilepsy or poorer seizure control in association with psychiatric disorders in people who have epilepsy. Mental health concerns are important for everyone. An accurate, undistorted understanding of the relation between mental health disorders and epilepsy is essential to ensure appropriate therapy and to avoid unnecessary and potentially harmful treatments and common misconceptions.

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Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies.

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Comment in

BMJ. 2016;353:i1965.

OBJECTIVE: To test previous signals of a risk of orofacial cleft (OC) and clubfoot with exposure to the antiepileptic lamotrigine, and to investigate risk of other congenital anomalies (CA).

METHODS: This was a population-based case-malformed control study based on 21 EUROCAT CA registries covering 10.1 million births (1995-2011), including births

to 2005 in which the clubfoot signal was generated and a subsequent independent study population of 6.3 million births. A total of 226,806 babies with CA included livebirths, stillbirths, and terminations of pregnancy following prenatal diagnosis. First-trimester lamotrigine monotherapy exposure in OC cases and clubfoot cases was compared to other nonchromosomal CA (controls). Odds ratios (OR) were adjusted for registry. An exploratory analysis compared the proportion of each standard EUROCAT CA subgroup among all babies with nonchromosomal CA exposed to lamotrigine monotherapy with non-AED exposed pregnancies.

RESULTS: There were 147 lamotrigine monotherapy-exposed babies with nonchromosomal CA. For all OC, OR_{adj} was 1.31 (95% confidence interval [CI] 0.73-2.33), isolated OC 1.45 (95% CI 0.80-2.63), isolated cleft palate 1.69 (95% CI 0.69-4.15). Overall OR_{adj} for clubfoot was 1.83 (95% CI 1.01-3.31) and 1.43 (95% CI 0.66-3.08) in the independent study population. No other specific CA were significantly associated with lamotrigine monotherapy.

CONCLUSIONS: The risk of OC was not significantly raised and we estimate the excess risk of OC to be less than 1 in every 550 exposed babies. We have not found strong independent evidence of a risk of clubfoot subsequent to our original signal. Our study cannot assess the general malformation risk among lamotrigine-exposed pregnancies.

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Obesity and overweight as CAE comorbidities and differential drug response modifiers.

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OBJECTIVE: This study examined whether overweight and obesity are pretreatment comorbidities and predictors of short-term drug response in newly diagnosed untreated childhood absence epilepsy (CAE). We also examined whether dietary intake accounts for observed pretreatment body mass index (BMI) distribution.

METHODS: Pretreatment height and weight were available for 445 of 446 participants in the NIH-funded CAE comparative effectiveness trial (NCT00088452). Twenty-four-hour dietary recalls were collected. Calculated BMI and dietary intake were standardized for age, sex, and race/ethnicity and compared to age-matched US population from the National Health and Nutrition Examination Survey (NHANES). Logistic regression models tested BMI as a predictor of treatment response. Pharmacokinetic variables were explored as contributors to differential drug response.

RESULTS: After standardizing for demographic differences, children with CAE were more likely to be overweight (19.3% vs 13.8%; $p < 0.001$) or obese (14.5% vs 11.5%; $p < 0.001$) than NHANES controls. The combined prevalence of overweight and obesity was 33.8% in the CAE cohort and 25.3% among controls ($p < 0.001$). Mean daily energy intake (difference -79.5 kcal/day, $p = 0.04$) and daily carbohydrate intake (difference -10.7 g/day, $p = 0.04$) were lower in the CAE group than in NHANES controls. With increasing baseline BMI z score, the efficacy and effectiveness of ethosuximide and valproic acid over lamotrigine became more pronounced, despite no significant differences in drug exposure and trough levels.

CONCLUSIONS: Overweight and obesity are more prevalent in children with newly diagnosed CAE than in age-matched peers, despite lower caloric and carbohydrate intake. Baseline BMI may also predict differential drug response, which cannot be attributed to pharmacokinetic differences.

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Postmarketing experience with brivaracetam in the treatment of epilepsies: A multicenter cohort study from Germany.

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OBJECTIVE: To evaluate factors predicting efficacy, retention, and tolerability of add-on brivaracetam (BRV) in clinical practice.

METHODS: A multicenter, retrospective cohort study recruiting all patients who started BRV between February and November 2016 with observation time between 3 and 12 months.

RESULTS: Of a total of 262 patients (mean age 40, range 5-81 years, 129 male) treated with BRV, 227 (87%) were diagnosed to have focal, 19 (7%) idiopathic generalized and 8 (3%) symptomatic generalized epilepsy, whereas 8 (3%) were unclassified. The length of exposure to BRV ranged from 1 day to 12 months, with a median retention time of 6.1 months, resulting in a total exposure time to BRV of 1,504 months. The retention rate was 79.4% at 3 months and 75.8% at 6 months. Efficacy at 3 months was 41.2% (50% responder rate) with 14.9% seizure-free for 3 months and, at 6 months, 40.5% with 15.3% seizure-free. Treatment-emergent adverse events were observed in 37.8% of the patients, with the most common being somnolence, dizziness, and behavioral adverse events (BAEs). BAE that presented under previous levetiracetam (LEV) treatment improved upon switch to BRV in 57.1% (20/35) and LEV-induced somnolence improved in 70.8% (17/24). Patients with BAE on LEV were more likely to develop BAE on BRV (odds ratio [OR] 3.48, 95% confidence interval [CI] 1.53-7.95).

SIGNIFICANCE: BRV in broad clinical postmarketing use is a well-tolerated anticonvulsant drug with 50% responder rates, similar to those observed in the regulatory trials, even though 90% of the patients included had previously been exposed to LEV. An immediate switch from LEV to BRV at a ratio of 10:1 to 15:1 is feasible. The only independent significant predictor of efficacy was the start of BRV in patients not currently taking LEV. The occurrence of BAE during previous LEV exposure predicted poor psychobehavioral tolerability of BRV treatment. A switch to BRV can be considered in patients with LEV-induced BAE.

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Prevalence and risk factors of seizure clusters in adult patients with epilepsy.

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PURPOSE: In the current study, we explored the prevalence of physician-confirmed seizure clusters. We also investigated potential clinical factors associated with the occurrence of seizure clusters overall and by epilepsy type.

METHODS: We reviewed medical records of 4116 adult (≥ 16 years old) outpatients with epilepsy at our centers for documentation of seizure clusters. Variables

including patient demographics, epilepsy details, medical and psychiatric history, AED history, and epilepsy risk factors were then tested against history of seizure clusters. Patients were then divided into focal epilepsy, idiopathic generalized epilepsy (IGE), or symptomatic generalized epilepsy (SGE), and the same analysis was run.

RESULTS: Overall, seizure clusters were independently associated with earlier age of seizure onset, symptomatic generalized epilepsy (SGE), central nervous system (CNS) infection, cortical dysplasia, status epilepticus, absence of 1-year seizure freedom, and having failed 2 or more AEDs ($P < 0.0026$). Patients with SGE (27.1%) were more likely to develop seizure clusters than patients with focal epilepsy (16.3%) and IGE (7.4%; all $P < 0.001$). Analysis by epilepsy type showed that absence of 1-year seizure freedom since starting treatment at one of our centers was associated with seizure clustering in patients across all 3 epilepsy types. In patients with SGE, clusters were associated with perinatal/congenital brain injury. In patients with focal epilepsy, clusters were associated with younger age of seizure onset, complex partial seizures, cortical dysplasia, status epilepticus, CNS infection, and having failed 2 or more AEDs. In patients with IGE, clusters were associated with presence of an aura. Only 43.5% of patients with seizure clusters were prescribed rescue medications.

CONCLUSION: Patients with intractable epilepsy are at a higher risk of developing seizure clusters. Factors such as having SGE, CNS infection, cortical dysplasia, status epilepticus or an early seizure onset, can also independently increase one's chance of having seizure clusters.

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Corpus Callosotomy for Intractable Epilepsy Revisited: The Children's Hospital of Michigan Series.

Luat AF(1),(2), Asano E(1),(2), Kumar A(3), Chugani HT(1),(2),(3),(4),(5), Sood S(6).

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Corpus callosotomy is a palliative procedure performed to reduce the severity of drug-resistant epilepsy. The authors assessed its efficacy on different seizure types in 20 subjects (age range 5-19 years); 8 with active vagus nerve stimulator. Fifteen had complete callosotomy, 3 had anterior 2/3, and 2 had

anterior 2/3 followed later by complete callosotomy. Ten had endoscopic approach. In all, 65% had $\geq 50\%$ reduction of generalized seizures leading to falls (atonic, tonic, myoclonic); 35% became seizure-free (follow-up period: 6 months to 9 years; mean 3 years). Seizure outcome distribution was better for generalized than for partial seizures ($P = .003$). Endoscopic approach was as effective as transcranial approach. Seven subjects who failed vagus nerve stimulator therapy responded with $\geq 50\%$ seizure reduction. Corpus callosotomy is an effective treatment for intractable generalized epilepsy leading to falls with significant seizure reduction or even elimination of seizures, in the majority of children.

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Diagnostic and Therapeutic Management of a First Unprovoked Seizure in Children and Adolescents With a Focus on the Revised Diagnostic Criteria for Epilepsy.

Sansevere AJ(1), Avalone J(1), Strauss LD(2), Patel AA(1), Pinto A(1), Ramachandran M(3), Sanchez Fernandez I(3), Bergin AM(1), Kimia A(4), Pearl PL(1), Loddenkemper T(1).

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By definition, unprovoked seizures are not precipitated by an identifiable factor, such as fever or trauma. A thorough history and physical examination are essential to caring for pediatric patients with a potential first unprovoked seizure. Differential diagnosis, EEG, neuroimaging, laboratory tests, and initiation of treatment will be reviewed. Treatment is typically initiated after 2 unprovoked seizures, or after 1 seizure in select patients with distinct epilepsy syndromes. Recent expansion of the definition of epilepsy by the ILAE allows for the diagnosis of epilepsy to be made after the first seizure if the clinical presentation and supporting diagnostic studies suggest a greater than 60% chance of a second seizure. This review summarizes the current literature on the diagnostic and therapeutic management of first unprovoked seizure in children and adolescents while taking into consideration the revised diagnostic criteria of epilepsy.

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Long-term outcomes of epilepsy surgery in tuberous sclerosis complex.

Liang S(1),(2), Zhang J(3), Yang Z(4), Zhang S(5), Cui Z(6), Cui J(5), Zhang J(5),(7), Liu N(5), Ding P(6),(5).

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Approximately 50% of patients with tuberous sclerosis complex (TSC) present intractable epilepsy, and surgery is an option for those patients. Hereby, we analyze long-term seizure control and neuropsychological outcomes of epilepsy surgery in patients with TSC. Clinical data were retrospectively collected from 66 patients with TSC and epilepsy followed up over 5 years, 51 of whom underwent epilepsy surgery between 2001 and 2011. Reductions in the number of seizures were analyzed at 1-year (1FU), 5-year (5FU), and 10-year (10FU) follow-up visits after the operation. Influential factors on postoperative seizure free and intelligence quotient (IQ) and quality-of-life (QOL) outcomes were evaluated at 5FU. Resective procedures included 26 tuber resections, 15 lobectomies, and 10 tuber resections and lobectomies. Corpus callosotomies were performed as the adjunctive approach in 11 cases with low IQ. The percentages of seizure-free cases were 74.5% at 1FU, 58.8% at 5FU, and 47.8% at 10FU, and the predictive factor for long-term postoperative seizure freedom was the history of preoperative seizures and preoperative full-scale IQ. Significant improvements were found in performance IQ, full-scale IQ, and QOL in patients from the surgery group, particularly those who were seizure free after the operation. Our study showed that epilepsy surgery in TSC with epilepsy rendered improvements in seizure control, full-scale IQ, and QOL. Satisfactory long-term seizure control was often achieved with an early operation and without mental retardation, and improvements in QOL and IQ were frequently observed in postoperative patients who remained seizure free.

Neurology. 2017 Jan 3;88(1):78-86. doi: 10.1212/WNL.0000000000003453. Epub 2016 Dec 2.

Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians.

Chen CB(1), Hsiao YH(1), Wu T(1), Hsieh MS(1), Tassaneeyakul W(1), Jorns TP(1), Sukasem C(1), Hsu CN(1), Su SC(1), Chang WC(1), Hui RC(1), Chu CY(1), Chen YJ(1), Wu CY(1), Hsu CK(1), Chiu TM(1), Sun PL(1), Lee HE(1), Yang CY(1), Kao PH(1), Yang CH(1), Ho HC(1), Lin JY(1), Chang YC(1), Chen MJ(1), Lu CW(1), Ng CY(1), Kuo KL(1), Lin CY(1), Yang CS(1), Chen DP(1), Chang PY(1), Wu TL(1), Lin YJ(1), Weng YC(1), Kuo TT(1), Hung SI(1), Chung WH(2); Taiwan Severe Cutaneous Adverse Reaction Consortium.

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Chen MJ, Lu CW, Ng CY, Kuo KL, Lin CY, Yang CS, Chen DP, Chang PY, Wu TL, Lin YJ, Weng YC, Kuo TT, Hung SI, Chung WH.

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OBJECTIVE: To investigate the risk and genetic association of oxcarbazepine-induced cutaneous adverse reactions (OXC-cADRs), including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), in Asian populations (Chinese and Thai).

METHODS: We prospectively enrolled patients with OXC-cADRs in Taiwan and Thailand from 2006 to 2014, and analyzed the clinical course, latent period, drug dosage, organ involvement, complications, and mortality. We also investigated the carrier rate of HLA-B*15:02 and HLA-A*31:01 of patients with OXC-cADRs and compared to OXC-tolerant controls. The incidence of OXC-SJS/TEN was compared with carbamazepine (CBZ)-induced SJS/TEN according to the nationwide population dataset from the Taiwan National Health Insurance Research Database.

RESULTS: We enrolled 50 patients with OXC-cADRs, including 20 OXC-SJS/TEN and 6 drug reaction with eosinophilia and systemic symptoms, of Chinese patients from Taiwan and Thai patients from Thailand. OXC-cADRs presented with less clinical severity including limited skin detachment (all $\leq 5\%$) and no mortality. There was a significant association between HLA-B*15:02 and OXC-SJS ($p = 1.87 \times 10^{-10}$); odds ratio 27.90; 95% confidence interval [CI] 7.84-99.23) in Chinese and this significant association was also observed in Thai patients. The positive and negative predictive values of HLA-B*15:02 for OXC-SJS/TEN were 0.73% and 99.97%, respectively. HLA-A*31:01 was not associated with OXC-cADRs. The incidence and mortality of OXC-SJS/TEN was lower than CBZ-SJS/TEN in new users ($p = 0.003$; relative risk 0.212; 95% CI 0.077-0.584).

CONCLUSIONS: Our findings suggest that HLA-B*15:02 is significantly associated with OXC-SJS in Asian populations (Chinese and Thai). However, the severity and incidence of OXC-SJS/TEN are less than that of CBZ-SJS/TEN. The need for preemptive HLA-B*15:02 screening should be evaluated further.

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Common and Distinctive Patterns of Cognitive Dysfunction in Children With Benign Epilepsy Syndromes.

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BACKGROUND: Childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes are the most common forms of benign epilepsy syndromes. Although cognitive dysfunctions occur in children with both childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes, the similarity between their patterns of underlying cognitive impairments is not well understood. To describe these patterns, we examined multiple cognitive functions in children with childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes.

METHODS: In this study, 43 children with childhood absence epilepsy, 47 children with benign childhood epilepsy with centrotemporal spikes, and 64 control subjects were recruited; all received a standardized assessment (i.e., computerized test battery) assessing processing speed, spatial skills, calculation, language ability, intelligence, visual attention, and executive function. Groups were compared in these cognitive domains. Simple regression analysis was used to analyze the effects of epilepsy-related clinical variables on cognitive test scores.

RESULTS: Compared with control subjects, children with childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes showed cognitive deficits in intelligence and executive function, but performed normally in language processing. Impairment in visual attention was specific to patients with childhood absence epilepsy, whereas impaired spatial ability was specific to the children with benign childhood epilepsy with centrotemporal spikes. Simple regression analysis showed syndrome-related clinical variables did not affect cognitive functions.

CONCLUSIONS: This study provides evidence of both common and distinctive cognitive features underlying the relative cognitive difficulties in children with childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes. Our data suggest that clinicians should pay particular attention to the specific cognitive deficits in children with childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes, to allow for more discriminative and potentially more effective interventions.

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Juvenile myoclonic epilepsy as a spectrum disorder: A focused review.

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In consequence of newer research juvenile myoclonic epilepsy (JME) is no longer seen as a homogeneous disease. The causes of the existing variance are only partially known yet. We discuss to what extent the phenotypical spectrum of this polygenetically determined disorder expresses genetically defined endophenotypes, or is due to mere quantitative differences in the expression of the core phenotype. Of the three common seizure types of JME, myoclonic, generalized tonic-clonic and absences, absences also occur independently and are strong candidates for an endophenotype. Focal features may in some patients be seen in clinical seizures or the EEG but rarely in both. They have no morphological correlates. In a system epilepsy, local manifestations are possible, and some are due to reflex mechanisms. Of the four reflex epileptic traits common in JME, photosensitivity and praxis induction appear related to basic mechanisms of the core syndrome, whereas language-induced orofacial reflex myocloni and eye closure sensitivity are also seen in other clinical contexts and therefore seem to represent endophenotypes. Cognitive abnormalities indicating slight frontal lobe dysfunction seem to be ubiquitous in JME and are also seen in unaffected siblings of patients. Cluster B personality disorder is found in 1/3 of patients, representing a more severe expression of the underlying pathology. Treatment response and prognosis seem to be affected by an interplay of the described factors producing the severest end of the JME spectrum. The spectrum appears to be due to an interaction of stronger or weaker expression of the core phenotype with various endophenotypes.

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Photosensitivity and epilepsy: Current concepts and perspectives-A narrative review.

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The authors review the influence of photic stimuli on the generation of epileptic seizures, addressing the first descriptions of the phenomenon and its subsequent exploration. Initially defined in the 1950's, links between intermittent photic stimulation (IPS) and seizures were well understood by the 1970. Since then the increasing exposure to photic stimuli associated with modern life (for instance through TVs, patterns, computer games and electronic instruments with flickering

displays) has led to an increased interest in this issue. Diverse stimulation procedures have been described and difference in the effects of stimulation frequencies and types, colour and lighting have been recognised. Approximately 5% of patients with epilepsy have photosensitive epilepsy (PSE). PSE is commoner in younger individuals, more frequent in women, often time-limited, generally easy to treat and closely related to generalised epilepsies, especially Juvenile Myoclonic Epilepsy (JME). Structural and functional studies of PSE indicate abnormalities beyond the frontal lobes and evidence for the role of the visual cortex in human PSE. A reduction in connectivity between prefrontal and frontopolar regions and increased connectivity between occipital cortex and the supplementary motor area may be the basis for triggering motor seizures in JME. Due to the changes observed in such areas, it is hypothesised that photoparoxysmal responses (PPR) could be a final expression of pathogenic phenomena in the striato-thalamocortical system, and possibly a core feature of JME as system epilepsy. The familial transmission of epileptiform responses to IPS is well-recognised, but no clear relation between PSE and specific genes has emerged. Although the influence of ethnic factors on PSE has been widely studied, clear conclusions are still lacking. Pharmacological therapeutic approaches are beyond the scope of this review although preventive measures allowing patients to avoid PS seizure initiation and/or generalisation are discussed. Given the gender/age group most commonly affected by PSE, the risks and benefits of drug treatment need to be carefully weighed up.

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Psychiatric comorbidities in new onset epilepsy: Should they be always investigated?

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The new definition of epilepsy establishes that epilepsy is not only a disorder presenting with epileptic seizures but it can be often associated with cognitive and psychiatric comorbidities. In fact, the prevalence of psychiatric comorbidities is relatively high in patients with epilepsy (PWE), as one in three patients will have experienced a psychiatric disorder in the course of their life, with mood and anxiety disorders being the most frequent. Psychiatric comorbidities often precede the onset of the seizure disorder, and affect the life of these patients and the course of the seizure disorder at several levels, including a worse tolerance of pharmacotherapy with antiepileptic drugs (AEDs), in particular the development of iatrogenic psychiatric symptoms from pharmacologic and surgical treatments, an increased mortality risk, a worse quality of life and higher economic burdens of the patient, family and society as a whole. Accordingly, psychiatric comorbidities should be recognized at the time of the initial evaluation of every PWE and their treatment needs to be

incorporated within the overall therapeutic plan. This question is addressed in this article.

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Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy.

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OBJECTIVE: To ascertain possible determinants of carbamazepine (CBZ)- and oxcarbazepine (OXC)-induced hyponatremia in a large cohort of people with epilepsy.

METHODS: We collected data on serum sodium levels in people with epilepsy who were attending a tertiary epilepsy center while on treatment with CBZ or OXC. We defined hyponatremia as $\text{Na}^+ \leq 134$ mEq/L and severe hyponatremia as $\text{Na}^+ \leq 128$ mEq/L.

RESULTS: We identified 1,782 people who had used CBZ ($n = 1,424$) or OXC ($n = 358$), of whom 50 were treated with both drugs. Data on sodium level measurements were available in 1,132 on CBZ and in 289 on OXC. Hyponatremia occurred in 26% of those taking CBZ and 46% of those taking OXC. This was severe in 7% in the CBZ group and 22% in the OXC group. Hyponatremia was symptomatic in 48% and led to admissions in 3%. Age over 40 years, high serum levels of CBZ and OXC, and concomitant use of other antiepileptic drugs were the main risk factors for hyponatremia in both treatment groups. Female patients on OXC were at a higher risk than male patients of hyponatremia. The risk of hyponatremia on CBZ was significantly associated with the risk of hyponatremia on OXC within a subgroup that used both drugs consecutively.

SIGNIFICANCE: Hyponatremia is a common problem in people taking CBZ or OXC. Regular ascertainment of sodium levels in those taking either drug is recommended and results should be acted on.

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Welfare consequences for people with epilepsy and their partners: A matched nationwide study in Denmark.

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PURPOSE: We aimed to evaluate the excess direct and indirect costs associated with epilepsy.

METHODS: From the Danish National Patient Registry (1998-2013), we identified people within all ages with an epilepsy diagnosis and matched them to control individuals. Additionally, partners of people with epilepsy were identified, who were compared with control partners. Direct costs included frequencies and costs of hospitalizations and weighted outpatient use according to diagnosis-related group, and specific outpatient costs based on data from the Danish Ministry of Health. The use and costs of drugs were based on data from the Danish Medicines Agency. The frequencies of visits and hospitalizations, and costs from general practice were derived from data from the National Health Security. Indirect costs included labor supply-based income data, and all social transfer payments obtained from Coherent Social Statistics.

RESULTS: A greater percentage of people with epilepsy and their partners compared with respective control subjects received social services (sick pay or disability pension). Those with epilepsy had a lower employment rate than did controls for equivalent periods up to eight years before the diagnosis was made. Mortality was significantly higher in people with epilepsy than in control individuals (hazard ratio 2.38 (95% CI: 2.34, 2.41)). The additional direct and indirect annual costs of epilepsy compared with controls were € for persons with epilepsy and €2494 for their partners.

CONCLUSION: Epilepsy has major socioeconomic consequences for individual patients, their partners and society.

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Comparative effectiveness of eight antiepileptic drugs in adults with focal refractory epilepsy: the influence of age, gender, and the sequence in which drugs were introduced onto the market.

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The first objective was to determine the long-term retention rate of eight antiepileptic drugs (AEDs) commonly used as adjunctive therapy in adults with focal refractory epilepsy. Second, we assessed the effects of age and gender on retention rates. Third, we examined if the retention rate could be influenced by the sequence in which the AEDs had entered the market. Patients with focal refractory epilepsy treated with any of the eight AEDs in Tampere University Hospital were identified retrospectively (N = 507). Retention rates were evaluated with the Kaplan-Meier method. Follow-up started at the first date of treatment and each individual was followed a maximum of 36 months. We calculated the following 3-year retention rates: lacosamide 77.1% (N = 137), lamotrigine 68.3% (N = 177), levetiracetam 66.7% (N = 319), clobazam 65.6% (N = 130), topiramate 61.6% (N = 178), zonisamide 60.4% (N = 103), pregabalin 54.6% (N = 127), and gabapentin 40.2% (N = 66). Lacosamide, levetiracetam, and clobazam were the most effective AEDs in the elderly. The retention rate for pregabalin was higher in males (65%) than females (51%) whereas females had higher retention rates for both topiramate (72 vs. 58%) and zonisamide (67 vs. 57%). The retention rate was influenced by the sequence in which these AEDs entered the market. We provide important information about practical aspects of these eight AEDs, revealing that there are differences in their effectiveness as adjunctive treatment for focal refractory epilepsy. Most importantly, the retention rate appears to be influenced by the sequence in which these AEDs were introduced onto the market.

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Characteristics associated with quality of life among people with drug-resistant epilepsy.

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Quality of Life (QoL) is the preferred outcome in non-pharmacological trials, but there is little UK population evidence of QoL in epilepsy. In advance of evaluating an epilepsy self-management course we aimed to describe, among UK participants, what clinical and psycho-social characteristics are associated with QoL. We recruited 404 adults attending specialist clinics, with at least two seizures in the prior year and measured their self-reported seizure frequency, co-morbidity, psychological distress, social characteristics, including self-mastery and stigma, and epilepsy-specific QoL (QOLIE-31-P). Mean age was 42 years, 54% were female, and 75% white. Median time since diagnosis was 18 years, and 69% experienced ≥ 10 seizures in the prior year. Nearly half (46%) reported additional medical or psychiatric conditions, 54% reported current anxiety and 28% reported current depression symptoms at borderline or case level, with 63% reporting felt stigma. While a maximum QOLIE-31-P score is 100, participants' mean score was 66, with a wide range (25-99). In order of large to small magnitude: depression, low self-mastery, anxiety, felt stigma, a history of medical and psychiatric comorbidity, low self-reported medication adherence, and greater seizure frequency were associated with low QOLIE-31-P scores. Despite specialist care, UK people with epilepsy and persistent seizures experience low QoL. If QoL is the main outcome in epilepsy trials, developing and evaluating ways to reduce psychological and social disadvantage are likely to be of primary importance. Educational courses may not change QoL, but be one component supporting self-management for people with long-term conditions, like epilepsy.

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The prevalence of anxiety and associated factors in persons with epilepsy.

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The objectives of this study were to estimate the prevalence of, and factors associated with, anxiety in epilepsy. We conducted a cross-sectional analysis using data from the Neurological Disease and Depression Study. The prevalence of anxiety and associated factors were assessed using descriptive statistics and logistic regression. Of the total sample (n = 250 patients), nearly 40.0% of participants had anxiety according to the Hospital Anxiety and Depression Scale. The most prevalent symptom of anxiety was "worrying thoughts" (35.6%). After adjustment for age and sex, depression (odds ratio [OR] = 8.97, 95% confidence interval [CI] = 4.38-18.40), medication side effects (OR = 1.79, 95% CI = 1.04-3.05), smoking (OR = 4.35, 95% CI = 2.27-8.31), and illicit substance use (OR = 2.42, 95% CI = 1.18-4.96) were significantly associated with higher odds of anxiety, whereas higher education (OR = 0.47, 95% CI = 0.28-0.80) was associated with lower odds of anxiety. Furthermore, participants with anxiety reported more severe epilepsy, debilitating seizures, and overall lower quality of life. Evidence from our study reveals a high prevalence of anxiety in persons with epilepsy and that anxiety is associated with a variety of negative outcomes. These findings further emphasize the need for more studies to understand the impact of anxiety and its relationship with various sociodemographic and clinical factors.

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Prediction of specific depressive symptom clusters in youth with epilepsy: The NDDI-E-Y versus Neuro-QOL SF.

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OBJECTIVE: Proper assessment and early identification of depressive symptoms are essential to initiate treatment and minimize the risk for poor outcomes in youth with epilepsy (YWE). The current study examined the predictive utility of the Neurological Disorders Depression Inventory-Epilepsy for Youth (NDDI-E-Y) and the Neuro-QOL Depression Short Form (Neuro-QOL SF) in explaining variance in overall depressive symptoms and specific symptom clusters on the gold standard Children's

Depression Inventory-2 (CDI-2).

METHODS: Cross-sectional study examining 99 YWE (female 68, mean age 14.7 years) during a routine epilepsy visit, who completed self-report measures of depressive symptoms, including the NDDI-E-Y, CDI-2, and the Neuro-QOL SF. Caregivers completed a measure of seizure severity. All sociodemographic and medical information was evaluated through electronic medical record review.

RESULTS: After accounting for seizure and demographic variables, the NDDI-E-Y accounted for 45% of the variance in the CDI-2 Total score and the CDI-2 Ineffectiveness subscale. Furthermore, the NDDI-E-Y predicted CDI-2 Total scores and subscales similarly, with the exception of explaining significantly more variance in the CDI-2 Ineffectiveness subscale compared to the Negative Mood subscale. The NDDI-E-Y explained greater variance compared to Neuro-QOL SF across the Total (48% vs. 37%) and all CDI-2 subscale scores; however, the NDDI-E-Y emerged as a stronger predictor of only CDI-2 Ineffectiveness. Both the NDDI-E-Y and Neuro-QOL SF accounted for the lowest amount of variance in CDI-2 Negative Mood. Sensitivity was poor for the Neuro-QOL SF in predicting high versus low CDI-2 scores.

SIGNIFICANCE: The NDDI-E-Y has strong psychometrics and can be easily integrated into routine epilepsy care for quick, brief screening of depressive symptoms in YWE.

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Cognition in epilepsy patients with hypothalamic hamartomas.

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Many patients with epilepsy caused by hypothalamic hamartomas (HHs) have cognitive impairments during the course of the disease or following neurosurgical treatment. The purpose of this study was to assess cognitive function in these patients, as well as factors influencing preoperative cognitive performance and cognitive outcome after neurosurgical treatment. Using the two largest and most detailed neuropsychology datasets on HH and epilepsy from two centers, we retrospectively report on cognitive functions in 48 patients with structural epilepsy due to HH (mean age \pm standard deviation [SD] 20 ± 12 years, range 5-53 years, median 16 years; disease duration mean 17 ± 11 years). Intelligence, verbal learning and recall, and speed and executive functions (processing speed

and cognitive flexibility) were assessed before and on average 19 (\pm 11) months after surgery (interstitial radiosurgery: N = 22; neurosurgical resection/disconnection: N = 26). Prior to neurosurgical treatment, 52% of patients showed impaired executive and 62% showed reduced verbal memory functions. A trend for a detrimental effect of higher drug load on cognitive functioning was found. After neurosurgical treatment, intellectual functions for the entire cohort tended to increase. This correlated with improved seizure frequency and decreased number of antiepileptic drugs (AEDs). However, postoperative outcomes for individual patients were highly variable, with significant deteriorations in 17% (processing speed) to 34% (cognitive flexibility and verbal learning), and performance increases in 17% (intellectual functioning) up to 39% (processing speed) of the patients. Higher levels of presurgical performance were significant predictors of cognitive decline after surgery. These results are highly relevant for patient consultation and may help with therapeutic decisions.

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Epilepsy management in older people: Lessons from National Audit of Seizure management in Hospitals (NASH).

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PURPOSE: Epilepsy is the third most common diagnosis in older people, however management in this group remains variable. National Audit of Seizure management in Hospitals (NASH) set out to assess care provided to patients attending hospitals in England following a seizure.

METHOD: 154 Emergency Departments (EDs) across the UK took part. 1256 patients aged 60 years or over were included for analysis (median age 74 years, 54% men). 51% were known to have epilepsy, 17% had history of previous seizure or blackout and 32% presented with a suspected first seizure.

RESULTS: 14% of older patients with epilepsy were not on treatment, 59% were on monotherapy. Sodium valproate was the most commonly used antiepileptic, 28%. 35% of patients with epilepsy, aged 60 and over, had a CT during admission compared to only 17% of those under 60. 80% of patients aged 60 and over presenting with a likely first seizure were admitted to hospital, compared to 65% of those under 60. 34% of those with suspected first seizure were referred to a neurologist on discharge compared to 68% of patients under the age of 60. 52% of 60-69year olds

with a suspected first seizure were referred to neurology compared to 25% of patients aged 80-89.

CONCLUSIONS: Older patients presenting with seizures are more likely to be admitted to hospital and have imaging. They are less likely to be referred to specialist services on discharge. There appears to be significant disparity in patient age and rate of referral.

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Epilepsy surgery in patients older than 50 years: Effectiveness, safety, and predictors of outcome.

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PURPOSE: Surgery is an effective treatment for drug resistant focal epilepsy. Predictors of seizure outcome have been extensively addressed in the general population but similar data on older patients are still lacking. The aim of this

study is to evaluate effectiveness and safety of surgery for patients over 50 years and to investigate variables associated to seizure outcome.

METHODS: We performed a single center retrospective study including 50 patients over 50 years treated surgically for drug resistant focal epilepsy between 1997 and 2014. We analyzed the rate of success of seizure control, the association of several clinical variables with seizure outcome and the rate of surgery-related complications. We also investigated the impact of surgery on the patients' cognitive performances and mood profile.

RESULTS: At last follow-up 78% of our patients were seizure-free, similar to patients younger than 50 years operated on in the same period ($p=1$). The rate of surgery-related complications was 10%, higher compared to younger patients ($p<0.0001$). Pre-surgical daily seizure frequency ($p=0.0040$) and the histological diagnosis of LEAT ($p=0.0233$) were associated to a poorer seizure outcome. No significant differences were evidenced between pre- and postoperative neuropsychological profiles. A slight, not statistically significant improvement of the mood profile was observed postoperatively.

CONCLUSION: Our results suggest that surgery is an effective treatment option also for older epileptic patients, although it is burdened by a higher surgical risk as compared to younger patients. The availability of predictors of outcome also for these patients may be helpful for pre-surgical counseling.

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Hormone replacement therapy with estrogens may reduce lamotrigine serum concentrations: A matched case-control study.

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Lamotrigine (LTG) is an antiepileptic drug that is metabolized via glucuronidation. Since the glucuronidizing enzyme is inducible by estrogens, LTG serum concentrations may fall by 50-60% when combined with hormonal contraceptives that contain ethinyl estradiol (EE). Little is known about a possible interaction between estrogens used for hormone replacement therapy (HRT) and LTG, and the few available data are conflicting. Data from serum samples analyzed for LTG were therefore retrieved from a routine therapeutic drug monitoring database. Users of HRT and EE were identified and matched with controls for age and dose. No enzyme-inducing or enzyme-inhibiting comedication was allowed. LTG serum concentration-to-dose ratios (CDRs) were calculated. Case groups and their respective control groups were compared by the Mann-Whitney U test. Seventy-nine HRT users (dose range 1-4 mg/day) and 200 EE users (dose range 20-40 $\mu\text{g/day}$), as well as 158 and 400 matching controls, respectively, could be included. Both EE users and HRT users had significantly lower mean LTG CDRs than their respective matched controls. These results suggest that HRT with estrogens

may reduce serum LTG concentrations.

Epilepsia. 2017 Mar;58(3):356-362. doi: 10.1111/epi.13644. Epub 2016 Dec 18.

Ictal asystole: A systematic review.

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OBJECTIVE: To comprehensively analyze ictal asystole (IA) on a large number of subjects.

METHODS: We performed a systematic review of case report studies of patients diagnosed with IA (1983-2016). Each included case was characterized with respect to patient history, IA seizure characteristics, diagnostic workup, and therapy.

In addition, comparative analyses were also carried out: two alignments were developed based on the delay between epilepsy onset and IA onset ("new-onset" if <1 year, "late-onset" if ≥1 year) and asystole duration (asystole was "very prolonged" if lasted >30 s).

RESULTS: One hundred fifty-seven cases were included. All patients had focal epilepsy. In 7% of cases IA developed during a secondary generalized tonic-clonic seizure. Both the seizure-onset zone and the focal seizure activity at asystole beginning were usually temporal ($p < 0.001$ and $p = 0.001$, respectively) and were lateralized to the left hemisphere in 62% ($p = 0.005$ and $p = 0.05$, respectively). Asystole duration was 18 ± 14 s (mean±SD) (range 3-96 s); 73% of patients had late-onset, 27% had new-onset IA. Compared to late-onset IA, new-onset IA was associated with female gender ($p = 0.023$), preexisting heart condition ($p = 0.014$), focal seizure activity at asystole beginning ($p = 0.012$), normal neuroimaging ($p = 0.013$), normal interictal EEG ($p < 0.001$), auditory aura ($p = 0.012$), and drug-responsive epilepsy ($p < 0.001$). "Very prolonged" asystole was associated with secondary generalized tonic-clonic seizures ($p = 0.003$) and tended to occur in extratemporal lobe seizures ($p = 0.074$). No IA-related death was reported.

SIGNIFICANCE: Characteristics considered to be typical of IA (focal, left temporal seizures appearing on grounds of a long-lasting, intractable epilepsy) seem only partially legitimate. We suggest that in new-onset IA, female gender and a preexisting heart condition could serve as predispositions in an otherwise benign epilepsy. We speculate that in late-onset IA, male-predominant changes in neuronal networks in chronic, intractable epilepsy and an accompanying autonomic dysregulation serve as facilitating factors.

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Epilepsy and Pregnancy: For healthy pregnancies and happy outcomes. John Paul Leach on behalf of the multispecialty UK epilepsy mortality group.

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Between 2009 and 2012 there were 26 epilepsy-related deaths in the UK of women who were pregnant or in the first post-partum year. The number of pregnancy-related deaths in women with epilepsy (WWE) has been increasing. Expert assessment suggests that most epilepsy-related deaths in pregnancy were preventable and attributable to poor seizure control. While prevention of seizures during pregnancy is important, a balance must be struck between seizure control and the teratogenic potential of antiepileptic drugs (AEDs). A range of professional guidance on the management of epilepsy in pregnancy has previously been issued, but little attention has been paid to how optimal care can be delivered to WWE by a range of healthcare professionals. We summarise the findings of a multidisciplinary meeting with representation from a wide group of professional bodies. This focussed on the implementation of optimal pregnancy epilepsy care aiming to reduce mortality of epilepsy in mothers and reduce morbidity in babies exposed to AEDs in utero. We identify in particular -What stage to intervene - Golden Moments of opportunities for improving outcomes -Which Key Groups have a role in making change -When - 2020 vision of what these improvements aim to achieve. -How to monitor the success in this field We believe that the service improvement ideas developed for the UK may provide a template for similar initiatives in other countries.

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Epilepsy after cerebral infection: review of the literature and the potential for surgery.

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The risk of unprovoked seizures in population-based cohorts of cerebral infection survivors is 7-8% in developed countries, rising to considerably higher rates in resource-poor countries. The main risk factors for epilepsy after cerebral infection, besides acute seizures, are infection-associated brain lesions and status epilepticus during the acute phase. Despite the high prevalence of pharmacoresistant epilepsies after cerebral infections, especially in patients with MRI-identifiable lesions, only a small minority undergoes epilepsy surgery. However, excellent surgical candidates are particularly those with a history of meningitis or encephalitis in early childhood, hippocampal sclerosis on MRI, as well as a history, seizure semiology, and EEG-findings compatible with the diagnosis of a mesial temporal lobe epilepsy syndrome. More challenging are patients with neocortical/extratemporal lobe epilepsies post cerebral infection. Finally, patients with a severe hemispheric injury with contralateral hemiparesis are candidates for hemispherectomy/hemispherotomy. This review attempts to shed some light on this frequent cause of symptomatic focal epilepsy, with an emphasis

on the chances offered by epilepsy surgery.

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Instruction manual for the ILAE 2017 operational classification of seizure types.

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This companion paper to the introduction of the International League Against Epilepsy (ILAE) 2017 classification of seizure types provides guidance on how to employ the classification. Illustration of the classification is enacted by tables, a glossary of relevant terms, mapping of old to new terms, suggested abbreviations, and examples. Basic and extended versions of the classification

are available, depending on the desired degree of detail. Key signs and symptoms of seizures (semiology) are used as a basis for categories of seizures that are focal or generalized from onset or with unknown onset. Any focal seizure can further be optionally characterized by whether awareness is retained or impaired. Impaired awareness during any segment of the seizure renders it a focal impaired awareness seizure. Focal seizures are further optionally characterized by motor onset signs and symptoms: atonic, automatisms, clonic, epileptic spasms, or hyperkinetic, myoclonic, or tonic activity. Nonmotor-onset seizures can manifest as autonomic, behavior arrest, cognitive, emotional, or sensory dysfunction. The earliest prominent manifestation defines the seizure type, which might then progress to other signs and symptoms. Focal seizures can become bilateral tonic-clonic. Generalized seizures engage bilateral networks from onset. Generalized motor seizure characteristics comprise atonic, clonic, epileptic spasms, myoclonic, myoclonic-atonic, myoclonic-tonic-clonic, tonic, or tonic-clonic. Nonmotor (absence) seizures are typical or atypical, or seizures that present prominent myoclonic activity or eyelid myoclonia. Seizures of unknown onset may have features that can still be classified as motor, nonmotor, tonic-clonic, epileptic spasms, or behavior arrest. This "users' manual" for the ILAE 2017 seizure classification will assist the adoption of the new system.

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Progress report on new antiepileptic drugs: A summary of the Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII).

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The Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII) took place in Madrid, Spain, on June 26-29, 2016, and was attended by >200 delegates from 31 countries. The present Progress Report provides an update on experimental and clinical results for drugs presented at the Conference.

Compounds for which summary data are presented include an AED approved in 2016 (brivaracetam), 12 drugs in phase I-III clinical development (adenosine, allopregnanolone, bumetanide, cannabidiol, cannabidivarin, 2-deoxy-d-glucose,

everolimus, fenfluramine, huperzine A, minocycline, SAGE-217, and valnoctamide) and 6 compounds or classes of compounds for which only preclinical data are available (bumetanide derivatives, sec-butylpropylacetamide, FV-082, 1OP-2198, NAX 810-2, and SAGE-689). Overall, the results presented at the Conference show that considerable efforts are ongoing into discovery and development of AEDs with potentially improved therapeutic profiles compared with existing agents. Many of the drugs discussed in this report show innovative mechanisms of action and many have shown promising results in patients with pharmaco-resistant epilepsies, including previously neglected rare and severe epilepsy syndromes.

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A review of people who did not attend an epilepsy clinic and their clinical outcomes.

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PURPOSE: To review the clinical outcomes of people who failed to attend or failed subsequent follow up in a Primary Care based specialist epilepsy service.

METHOD: The case notes of 200 people who had failed to initially attend the service or subsequent follow up from 2005 to 2013 were reviewed.

RESULTS: Clinical outcomes were determined for 152 people, with the remaining 48 having left the area. For those not attending at all, 64% had no further recorded events, a further 22% came under alternative specialist care and were managed appropriately, 6% were already in remission at the time of referral or at follow up and stayed seizure free. For people attending, but were subsequently lost to follow up, 78% were in remission, had improved seizure frequency, and normal pregnancies. In total 6% of those with poor control came under subsequent Neurological care.

CONCLUSION: This study suggests that for the majority of people who fail to attend or are lost to follow up in a primary care specialist epilepsy clinic, the primary reasons appear to be that they had no further events, improved seizure control or that seizure remission has been achieved. The majority with persistent poor control came under Neurological care.

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Trends in Antiepileptic Drug Use in Children and Adolescents With Epilepsy.

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OBJECTIVE: We describe the trends in antiepileptic drug (AED) use in children and adolescents with epilepsy in the United States.

METHODS: We undertook a cross-sectional study based on Medicaid Analytic eXtract data set from 26 US states. Children and adolescents aged three to 18 years with at least one year continuous Medicaid fee-for-service coverage after the second outpatient or the first inpatient diagnosis of epilepsy in each calendar year during 1999 to 2009 were included in the study; therefore, 11 cohorts were established. A patient was defined as being exposed to a specific AED if he or she had at least one-day supply of the AED during the 1-year follow-up period. The annual prevalence of AEDs was reported, stratified by gender and age. The trends in AED use were evaluated through linear regression.

RESULTS: The sample sizes of the 11 cohorts ranged between 17,304 and 22,672. The annual prevalence of valproic acid use declined from 42.4% in 1999 to 26.5% in 2009, and the prevalence of carbamazepine use declined from 37.1% to 10.2%. Meanwhile, the prevalence of levetiracetam use increased from 5.1% to about 32.0% in 2009, and the prevalence of oxcarbazepine use increased from 1.3% to 19.1%. Since 2008, levetiracetam (29.6%) has replaced valproic acid (27.8%) as the most commonly used AED in children and adolescents with epilepsy. The prevalence of diazepam use increased from 11.6% to 28.1%.

SIGNIFICANCE: Compared with first- and second-generation antiepileptic drugs, third-generation AEDs have fewer adverse side effects, resulting in increased patient treatment adherence. Equally important is the economic impact of these newer AEDs. This first-of-its-kind study underscores the need for large database studies that objectively assess the cost-effectiveness of third-generation AEDs versus first- and second-generation AEDs in the treatment of childhood epilepsy.

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Epilepsy: Transition from pediatric to adult care. Recommendations of the Ontario epilepsy implementation task force.

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The transition from a pediatric to adult health care system is challenging for many youths with epilepsy and their families. Recently, the Ministry of Health and Long-Term Care of the Province of Ontario, Canada, created a transition working group (TWG) to develop recommendations for the transition process for patients with epilepsy in the Province of Ontario. Herein we present an executive summary of this work. The TWG was composed of a multidisciplinary group of pediatric and adult epileptologists, psychiatrists, and family doctors from academia and from the community; neurologists from the community; nurses and social workers from pediatric and adult epilepsy programs; adolescent medicine physician specialists; a team of physicians, nurses, and social workers dedicated to patients with complex care needs; a lawyer; an occupational therapist; representatives from community epilepsy agencies; patients with epilepsy; parents of patients with epilepsy and severe intellectual disability; and project managers. Three main areas were addressed: (1) Diagnosis and Management of Seizures; 2) Mental Health and Psychosocial Needs; and 3) Financial, Community, and Legal Supports. Although there are no systematic studies on the outcomes of transition programs, the impressions of the TWG are as follows. Teenagers at risk of poor transition should be identified early. The care coordination between pediatric and adult neurologists and other specialists should begin before the actual transfer. The transition period is the ideal time to rethink the diagnosis and repeat diagnostic testing where indicated (particularly genetic testing, which now can uncover more etiologies than when patients were initially evaluated many years ago). Some screening tests should be repeated after the move to the adult system. The seven steps proposed herein may facilitate transition, thereby promoting uninterrupted and adequate care for youth with epilepsy leaving the pediatric system.

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Insomnia in people with epilepsy: A review of insomnia prevalence, risk factors and associations with epilepsy-related factors.

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BACKGROUND: Insomnia is a common sleep complaint in the general population, and sleep loss may be a trigger for epileptic seizures.

OBJECTIVES: To conduct a comprehensive review of the literature of insomnia symptoms and insomnia disorder, their prevalence and epilepsy-related risk factors in people with epilepsy (PWE).

METHODS: A PUBMED search was performed for articles indexed to June 2016 involving human subjects, excluding papers in languages other than English, Spanish and Portuguese and case reports. Eligible studies were those using a clear definition of insomnia and reporting quantitative data on prevalence rates and risk factors. The search included the following terms: insomnia, sleep disorder(s), sleep disturbance(s) and sleep-wake in the title and abstract; and epilep* in the title. 425 papers were reviewed and 31 were selected for the final analysis (21 adult and 10 paediatric). Twenty-one studies used a control group. Two reviewer authors independently extracted all data and a third author resolved disagreements.

RESULTS: Most studies were hospital-based, cross-sectional and evaluated convenience samples representing highly select populations. Various insomnia inventories were used. Fourteen assessed insomnia (10 in adults, four, children), but only five as primary outcome (none in children). Four evaluated insomnia disorder based on international classification criteria (International Classification of Sleep Disorders - ICSD-2-in 3, and DSM-IV-TR, in 1). In adults, insomnia prevalence was 28.9-51% based on the Insomnia Severity Index ≥ 15 and 36-74.4% based on DSM-IV-TR or ICSD-2. The prevalence of insomnia in children was 13.1-31.5% using the Sleep Disturbance Scale for Children and 11% based on ICSD-2 diagnostic criteria. Compared to control groups, PWE usually had higher frequencies of insomnia symptoms and disorder. Insomnia was associated with greater impairment in quality of life and higher degree of depressive symptoms in several studies, and was inconsistently related to female gender, poor seizure control and antiepileptic drug polytherapy. In children, insomnia was associated with developmental delay, focal epilepsies and poor seizure control.

CONCLUSION: Insomnia symptoms and insomnia disorder are highly prevalent among PWE based on a limited number of studies with variable inclusion criteria and methodology. Excessive daytime sleepiness (EDS) was not found to be related to insomnia disorder or symptoms, and the exclusion of individuals with EDS may explain the higher frequencies of insomnia found in some studies. Additional investigations are needed given the potential impact of insomnia on seizure control, mood and QOL in PWE.

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Sleep abnormalities in juvenile myoclonic epilepsy-A sleep questionnaire and polysomnography based study.

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PURPOSE: To evaluate the quality of sleep, its architecture and occurrence of epileptiform discharges with their distribution across various stages of sleep in patients of Juvenile myoclonic epilepsy (JME), both drug naïve as well as those already on treatment.

METHODS: 99 patients of JME [36 drug naïve, 63 on antiepileptic drug(s) (AED)], and 30 healthy controls were recruited. Sleep quality and daytime sleepiness were evaluated with Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), respectively. Polysomnography (PSG) was done to assess the sleep architecture. The EDI (Epileptiform Discharge Index) per stage of sleep was calculated.

RESULTS: JME patients had significantly poor quality of sleep by PSQI ($p=0.02$). PSG revealed reduced sleep efficiency [$p<0.001$], increased sleep latency [$p=0.02$], increased% WASO [$p<0.001$], increased% N1 [$p=0.01$] and decreased% REM sleep [$p=0.002$] in the patients compared to controls. Epileptiform discharges were frequent among drug naïve JME patients [drug naïve, 868 vs. 727, treatment group]. EDI was higher in N1 ($p=0.001$) and N2 ($p=0.007$) in drug naïve compared to JME patients on treatment. EDI in valproate treatment group was relatively lower to other AEDs.

CONCLUSION: JME is associated with poor sleep quality and altered architecture, irrespective of treatment status. REM sleep is significantly decreased in JME patients. Epileptiform discharges are frequent in lighter NREM sleep and EDI is higher in drug naïve patients. Although AEDs disrupt the NREM sleep, their use is associated with arousal stability in lighter stages of sleep and lower EDI, in particular with valproate.

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Anion gap can differentiate between psychogenic and epileptic seizures in the emergency setting.

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Differentiation between psychogenic nonepileptic seizures (PNES) and generalized convulsive epileptic seizures (ES) is important for appropriate triaging in the emergency department (ED). This can be difficult in the ED, as the event is often not witnessed by a medical professional. In the current study, we investigated whether anion gap (AG), bicarbonate, and the Denver Seizure Score (DSS) could differentiate between PNES and ES. Of a total of 1,354 subjects reviewed from a tertiary care medical center, 27 PNES and 27 ES patients were identified based on clinical description and subsequent electroencephalogram. Multivariate logistic regression analysis and receiver operating characteristic curves were used to determine whether there was an association between seizure type and AG, bicarbonate, or DSS ($24\text{-bicarbonate} + 2 \times [\text{AG}-12]$) when samples were drawn within 24 h of the concerning event. The result showed that sensitivity and negative predictive value dropped markedly for all measures if samples were drawn >2 h after the event; the sensitivity was similar for AG and DSS and higher than for bicarbonate. We propose that $\text{AG} > 10$ (sensitivity of 81.8%, specificity of 100%) in the first 2 h after the event could be used as a potential tool in the ED to help differentiate between PNES and ES.

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Stress is associated with an increased risk of recurrent seizures in adults.

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OBJECTIVE: The literature is sparse on the complex interrelationships between stressors, depression, anxiety disorders, and epilepsy. We hypothesized that a relationship exists between stress and epilepsy. We evaluated whether markers of stress are associated with seizure recurrence in a low income community-based cohort of adults with single unprovoked seizure or newly diagnosed epilepsy.

METHODS: We ascertained adult residents of Northern Manhattan and Harlem, New York City, with a first unprovoked seizure or newly diagnosed epilepsy, between December 2010 and January 2013. At enrollment, we collected information about seizure phenomenology, demographics, clinical information, and measures of stress (environmental stress, stressful life events, facets of allostatic load-i.e., the cumulative effect of adaptation to stress, psychiatric disorders, and low collective efficacy). Collective efficacy assesses neighborhood characteristics and incorporates social cohesion and informal social control. All subjects were followed for 2 years for further seizures. Cox proportional hazard regression models were used to estimate the hazard ratios of seizure recurrence during the

2 years of follow-up.

RESULTS: We identified 52 subjects (64.2%) with a single unprovoked seizure and 29 (35.9%) with newly diagnosed epilepsy. Seizure recurrence was recorded in 38.5% (N = 20) of subjects with a single unprovoked seizure and in 69% of those with epilepsy (N = 20) ($p = 0.01$). In the overall sample, the hazard of seizure recurrence was increased by lifetime generalized anxiety disorder (3.0-fold) and by low collective efficacy (2.7-fold). In a second model, the hazard was increased by lifetime mood disorder (2.1-fold) and low collective efficacy (2.5-fold).

SIGNIFICANCE: Markers of stress (i.e., low collective efficacy, lifetime mood disorder, and lifetime generalized anxiety disorder) were associated with an increased risk for seizure recurrence in adults with a single unprovoked seizure or newly diagnosed epilepsy. Stress-reducing interventions, such as mindfulness, may be a useful, safe, and inexpensive adjunctive treatment for epilepsy.

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The incidence of SUDEP: A nationwide population-based cohort study.

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OBJECTIVE: To identify all cases of sudden unexpected death in epilepsy (SUDEP) among people in Sweden during 1 year and to determine the SUDEP incidence in relation to age, sex, and psychiatric comorbidity.

METHODS: We included all individuals with a hospital-based ambulatory care or hospital discharge diagnosis of epilepsy in the Swedish National Patient Registry during 1998-2005 who were alive on January 1, 2008. Deaths during 2008 were identified by linkage to the National Cause of Death Registry. Death certificates, medical charts, and police and autopsy reports were extensively reviewed to identify SUDEP cases.

RESULTS: Of 57,775 epilepsy patients alive on January 1, 2008, 1,890 died (3.3%) during 2008. Of these, 99 met the Annegers SUDEP criteria (49 definite, 19 probable, and 31 possible). SUDEP accounted for 5.2% of all deaths and 36% of deaths in the 0-15 years age group. The incidence of definite/probable SUDEP was 1.20/1,000 person-years, and higher in men (1.41) than in women (0.96). All SUDEP cases <16 years were in boys. SUDEP incidence at ages <16, 16-50, and >50 years was 1.11, 1.13, and 1.29, respectively, per 1,000 person-years. The incidence was

5-fold increased among female patients with psychiatric comorbidities compared to those without. Epilepsy was mentioned on the death certificate in only 62 of the 99 (63%) SUDEP cases.

CONCLUSIONS: Methods relying on death certificates underestimate SUDEP incidence. SUDEP risk has been underestimated especially in boys and in older people regardless of sex. Patients with psychiatric comorbidities, women in particular, are at increased SUDEP risk.

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Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study.

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OBJECTIVE: We designed a prospective, randomized, controlled, double-blind study to evaluate the efficacy of hippocampal deep brain stimulation (Hip-DBS) in patients with refractory temporal lobe epilepsy (TLE).

METHODS: Sixteen adult patients with refractory TLE were studied. Patient's workup included medical history, interictal and ictal electroencephalography (EEG), and high-resolution 1.5T magnetic resonance imaging (MRI). Patients were randomized on a 1:1 proportion to an active (stimulation on) or to a control (no stimulation) arm. After implantation, patients were allowed to recover for 1 month, which was followed by a 1-month titration (or sham) period. The 6-month blinded phase started immediately afterward. A postoperative MRI confirmed the electrode's position in all patients. All patients received bipolar continuous stimulation. Stimulus duration was 300 μ s and frequency was 130 Hz; final intensity was 2 V. Patients were considered responders when they had at least 50% seizure frequency reduction.

RESULTS: All patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 87% had focal aware seizures (FAS, simple partial seizures). Mean preoperative seizure frequency was 12.5 ± 9.4 (mean \pm standard deviation) per month. MRI findings were normal in two patients, disclosed bilateral mesial temporal sclerosis (MTS) in three, left MTS in five, and right MTS in six patients. An insertional effect could be noted in both control and active patients. In the active group ($n = 8$), four patients became seizure-free; seven of eight were considered responders and one was a nonresponder. There was a significant difference regarding FIAS frequency between the two groups from the first month of full stimulation ($p < 0.001$) until the end of the blinded phase ($p < 0.001$). This was also true for FAS, except for the third month of the blinded phase.

SIGNIFICANCE: Hip-DBS was effective in significantly reducing seizure frequency in patients with refractory TLE in the active group, as compared to the control group. Fifty-percent of the patients in the active group became seizure-free. The present study is the larger prospective, controlled, double-blind study to

evaluate the effects of Hip-DBS published to date.

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Antiepileptic drug discontinuation by people with epilepsy in the general population.

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OBJECTIVE: Rate, reasons, and predictors of antiepileptic drug (AED) discontinuation were investigated in a well-defined cohort of people with epilepsy to verify efficacy and tolerability of treatment up to 20 years from treatment initiation.

METHODS: The history of AED usage in children and adults with epilepsy registered

with 123 family physicians in an area of Northern Italy between 2000 and 2008 was recorded. Cumulative probabilities of AED withdrawal for specific reasons were estimated using cumulative incidence functions. The probabilities of withdrawing for terminal remission, and of achieving sustained remission while still on treatment, were also evaluated. The roles of sex, age at diagnosis, seizure types, duration at diagnosis, and syndrome were assessed with hazard ratios and 95% confidence intervals.

RESULTS: Seven hundred thirty-one of 747 individuals were treated with one or more AEDs during the disease course. The three commonest drugs were valproate, carbamazepine, and phenobarbital. Reported reasons for AED withdrawal were, in decreasing order, terminal remission, ineffectiveness, and adverse events. The probability of withdrawing the first AED for terminal remission was 1.0% at 1 year and increased to 20.0% at 20 years. Corresponding rates were 2.9% and 12.6% for ineffectiveness and 0.5% and 3.3% for adverse events. Reasons for withdrawal varied with individuals' age, sex, disease characteristics, and drugs.

SIGNIFICANCE: The initial AED given was retained in the majority of cases. Terminal remission, lack of efficacy, and adverse effects were, in decreasing order, the commonest reasons for AED discontinuation. Withdrawal could be predicted by age at diagnosis, sex, and clinical characteristics and varies among drugs.

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The impact of epilepsy on academic achievement in children with normal intelligence and without major comorbidities: A systematic review.

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PURPOSE: To systematically examine published literature which assessed the prevalence of academic difficulties in children with epilepsy (CWE) of normal intelligence, and its associating factors.

METHODS: A search was conducted on five databases for articles published in English from 1980 till March 2015. Included were studies who recruited children (aged 5-18 years), with a diagnosis or newly/recurrent epilepsy, an intelligent quotient (IQ) of ≥ 70 or attending regular school, with or without a control group, which measured academic achievement using a standardised objective measure, and published in English. Excluded were children with learning difficulties, intellectual disabilities (IQ <70) and other comorbidities such as attention deficits hyperactive disorder or autism. Two pairs of reviewers extracted the data, and met to resolve any differences from the data extraction

process.

RESULTS: Twenty studies were included. The majority of the studies assessed "low achievement" whilst only two studies used the IQ-achievement discrepancy definition of "underachievement". Fourteen studies (70%) reported that CWE had significantly lower academic achievement scores compared to healthy controls, children with asthma or reported norms. The remaining six studies (30%) did not report any differences. CWE had stable academic achievement scores over time (2-4 years), even among those whose seizure frequency improved. Higher parental education and children with higher IQ, and had better attention or had a positive attitude towards epilepsy, were associated with higher academic achievement score. Older children were found to have lower academic achievement score.

CONCLUSIONS: In CWE of normal intelligence, the majority of published literature found that academic achievement was lower than controls or reported norms. The high percentages of low achievement in CWE, especially in the older age group, and the stability of scores even as seizure frequency improved, highlights the need for early screening of learning problems, and continued surveillance.

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Status epilepticus-related etiology, incidence and mortality: A meta-analysis.

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Status epilepticus (SE) is a severe medical condition. To determine its epidemiology and outcome of SE, we performed a meta-analysis to investigate the etiology, incidence and mortality of SE. We searched PubMed and Embase between Jan 1, 2000, and Oct 31, 2016, with no regional restrictions, for observational studies of the etiology, incidence and mortality of SE. Forty-three studies were included in the meta-analysis. The pooled crude annual incidence rate, the pooled case fatality rate and the pooled crude annual mortality rate of SE were 12.6/100,000 (95% CI: 10.0-15.3), 14.9% (95% CI: 11.7-118.7) and 0.98/100,000 (95% CI: 0.74-1.22), respectively. Elderly subjects with SE had a higher case fatality rate (28.4% (95% CI: 17.7-42.3)) and crude annual incidence rate (27.1% (95% CI: 15.8-38.2)). The most important etiology-specific attributable fraction of patients with SE was acute symptomatic etiology (OR 0.411, 95% CI: 0.315-0.507). Age and economic income contributed to differences in SE incidence and short-term case fatality rate.

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Recurrence risk of ictal asystole in epilepsy.

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OBJECTIVE: To determine the recurrence risk of ictal asystole (IA) and its determining factors in people with epilepsy.

METHODS: We performed a systematic review of published cases with IA in 3 databases and additionally searched our local database for patients with multiple seizures simultaneously recorded with ECG and EEG and at least one IA. IA recurrence risk was estimated by including all seizures without knowledge of the chronological order. Various clinical features were assessed by an individual patient data meta-analysis. A random mixed effect logistic regression model was applied to estimate the average recurrence risk of IA. Plausibility of the calculated IA recurrence risk was checked by analyzing the local dataset with available information in chronological order.

RESULTS: Eighty patients with 182 IA in 537 seizures were included. Recurrence risk of IA amounted to 40% (95% confidence interval [CI] 32%-50%). None of the clinical factors (age, sex, type and duration of epilepsy, hemispheric lateralization, duration of IA per patient) appeared to have a significant effect on the short-term recurrence risk of IA. When considering the local dataset only, IA recurrence risk was estimated to 30% (95% CI 14%-53%). Information whether IA coincided with symptoms (i.e., syncope) or not was given in 60 patients: 100 out of 142 IAs were symptomatic.

CONCLUSION: Our data suggest that in case of clinically suspected IA, the recording of 1 or 2 seizures is not sufficient to rule out IA. Furthermore, the high short-term recurrence risk favors aggressive treatment, including pacemaker implantation if seizure freedom cannot be achieved.

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Underestimation of sudden deaths among patients with seizures and epilepsy.

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OBJECTIVE: To determine the definite and potential frequency of seizures and epilepsy as a cause of death (COD) and how often this goes unrecognized.

METHODS: Prospective determination of seizures or epilepsy and final COD for individuals aged 18-90 years with out-of-hospital sudden cardiac deaths (SCDs) from the population-based San Francisco POST SCD Study. We compared prospective seizure or epilepsy diagnosis and final COD as adjudicated by a multidisciplinary committee (pathologists, electrophysiologists, and a vascular neurologist) vs retrospective adjudication by 2 epileptologists with expertise in seizure-related mortality.

RESULTS: Of 541 SCDs identified during the 37-month study period (mean age 62.8 years, 69% men), 525 (97%) were autopsied; 39/525 (7.4%) had seizures or epilepsy (mean age: 58 years, range: 27-92; 67% men), comprising 17% of 231 nonarrhythmic sudden deaths. The multidisciplinary team identified 15 cases of epilepsy, 6 sudden unexpected deaths in epilepsy (SUDEPs), and no deaths related to acute symptomatic seizures. The epileptologists identified 25 cases of epilepsy and 8 definite SUDEPs, 10 possible SUDEPs, and 5 potential cases of acute symptomatic seizures as a COD.

CONCLUSIONS: Among the 25 patients identified with epilepsy by the epileptologists, they found definite or possible SUDEP in 72% (18/25) vs 24% (6/25) by the multidisciplinary group (6/15 cases they identified with epilepsy). The epileptologists identified acute symptomatic seizures as a potential COD in 5/14 patients with alcohol-related seizures. Epilepsy is underdiagnosed among decedents. Among patients with seizures and epilepsy who die suddenly, seizures and SUDEP often go unrecognized as a potential or definite COD.

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[Epub ahead of print]

Outcome of treatment changes in patients with drug-resistant chronic epilepsy: A tertiary center experience.

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BACKGROUND: Previous studies suggest that changing patients' anti-epileptic drug regimen can reduce the frequency of seizures. The approval of new anti-epileptic drugs with different modes of action during the last decades has provided multiple options for the treatment of epilepsy, although the efficacy of these new drugs is controversial. We aimed to determine the effects of adding or changing to a previously untried anti-epileptic drug, including recently approved drugs, on the frequency of seizures in patients with drug-resistant epilepsy.

METHODS: We analyzed treatment changes in drug-resistant patients at our outpatient clinic between 2010 and 2015. We classified patients' frequency of seizures after changes as freedom from seizures, $\geq 50\%$ reduction, $< 50\%$ reduction, no change, increase in seizures $< 50\%$ or increase in seizures $\geq 50\%$.

RESULTS: We analyzed 189 drug changes in 144 consecutive drug-resistant patients followed up for at least 6 months after the change; 138 changes involved administering newly marketed drugs: lacosamide (n=65), perampanel (n=30), eslicarbazepine (n=29), and retigabine (n=14). Changes resulted in freedom from seizures in 20 (13.9%) patients and in $\geq 50\%$ decrease in frequency in 55 (38.2%). The drugs most commonly associated with significant improvement (freedom from seizures or $\geq 50\%$ reduction) were lacosamide (39.3%), clobazam (11.2%), and levetiracetam (11.2%).

CONCLUSIONS: In patients with drug-resistant epilepsy, sequential changes increase the possibility of seizure control, and newer anti-epileptic drugs offer additional options for effective changes. Best combinations must be chosen taking into account drug, epilepsy and patient features.

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Concurrent mood and anxiety disorders are associated with pharmacoresistant seizures in patients with MTLE.

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OBJECTIVE: To investigate whether mood disorders (MD) and anxiety disorders (AD) are associated with seizure control in patients with mesial temporal lobe epilepsy (MTLE). We compared patients without any current psychiatric disorder, patients with current MD and/or AD, patients with subsyndromic depression episodes (SSDE) and anxiety episodes (SSAE), and patients with family psychiatric history.

METHODS: In a cross-sectional study, we included 144 consecutive patients with MTLE (82 pharmacoresistant and 62 treatment-responsive patients). Every patient underwent a psychiatric evaluation including the Structured Clinical Interview

for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Axis I (SCID-I), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), and Interictal Dysphoric Disorder Inventory (IDDI). Patients were divided into four groups: PsychNeg (G1, n = 61), current SSDE and SSAE (G2, n = 26), Current MD or AD (G3, n = 25), and current mixed MD/AD (G4, n = 32).

RESULTS: Among patients with pharmaco-resistant MTLE, 68.3% (56/82) experienced symptoms of depression and/or anxiety (G2, G3, and G4) (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.41-5.53, $p < 0.01$). Patients with mixed MD/AD (G4, n = 24/32) were more likely to have pharmaco-resistant MTLE (OR 4.04, 95% CI 1.57-10.42, $p < 0.01$) than psychiatric asymptomatic patients (G1, n = 26/61), and their seizure frequency was significantly higher ($p < 0.01$). Positive family psychiatric history was more frequent in pharmaco-resistant patients (n = 27/82, OR 2.28, 95% CI 1.02-5.05, $p = 0.04$). Finally, 31.6% of patients with MD and or AD were not receiving psychiatric treatment.

SIGNIFICANCE: Identification of comorbid MD/AD and of family psychiatric history is of the essence in patients with MTLE, as they appear to be associated with worse seizure control.

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Cognitive functioning in children with self-limited epilepsy with centrotemporal spikes: A systematic review and meta-analysis.

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OBJECTIVE: It is now well appreciated that benign epilepsy with centrotemporal spikes (BECTS, or more recently, ECTS) is associated with a range of cognitive and behavioral disturbances. Despite our improved understanding of cognitive functioning in ECTS, there have been to date no efforts to quantitatively synthesize the available literature within a comprehensive cognitive framework.

METHODS: The present systematic review and meta-analysis was conducted according to PRISMA guidelines. Forty-two case-control samples met eligibility criteria comprising a total of 1,237 children with ECTS and 1,137 healthy control children. Univariate, random-effects meta-analyses were conducted on eight cognitive factors in accordance with the Cattell-Horn-Carroll model of intelligence.

RESULTS: Overall, children with ECTS demonstrated significantly lower scores on neuropsychological tests across all cognitive factors compared to healthy controls. Observed effects ranged from 0.42 to 0.81 pooled standard deviation units, with the largest effect for long-term storage and retrieval and the smallest effect for visual processing.

SIGNIFICANCE: The results of the present meta-analysis provide the first clear evidence that children with ECTS display a profile of pervasive cognitive difficulties and thus challenge current conceptions of ECTS as a benign disease or of limited specific or localized cognitive effect.

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Long-term applicability of the new ILAE definition of epilepsy. Results from the PRO-LONG study.

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OBJECTIVE: The new epilepsy definition adopted by the International League Against Epilepsy (ILAE) includes patients with one unprovoked seizure with a probability of further seizures, similar to the general recurrence risk after two unprovoked seizures, occurring in a 10-year period. Long-term follow-up of patients diagnosed after a single seizure is needed to assess the applicability of the new epilepsy definition in clinical practice.

METHODS: Patients with newly diagnosed epilepsy were recruited retrospectively with a minimum follow-up of 10 years. Patients were stratified in two groups depending on the occurrence of one (new definition, ND) or two or more unprovoked seizures (traditional definition, TD) at the time of epilepsy diagnosis and compared for disease characteristics and factors predicting seizure recurrence. The primary outcome was the occurrence of a new unprovoked seizure during follow-up in the ND group. The secondary outcome was the achievement of an early remission in both groups.

RESULTS: Among 1,006 patients with newly diagnosed epilepsy, 152 (15.1%) were diagnosed after a single seizure. Compared to patients diagnosed using the TD, patients diagnosed according to the ND showed a higher proportion of subjects with an abnormal neurologic examination (19.9% vs. 13.7%, $p = 0.0504$) and with focal seizures (69.3% vs. 60.4%, $p = 0.0021$). The two samples differed in the presence of at least one of the factors predicting seizure recurrence (focal seizures or abnormal findings in at least one among the following: neurologic examination, electroencephalography [EEG], and neuroimaging) (94.6% vs. 89.1%, $p = 0.0376$). Long-term recurrence in patients diagnosed with the new definition

was 83.6% at 10 years and 89.1% at 15 years. The probability of early remission did not differ between the two groups.

SIGNIFICANCE: Our results support the applicability of the new epilepsy definition in clinical practice. Individual patient characteristics and a personalized diagnostic approach can justify treatment after a single unprovoked seizure.

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European Academy of Paediatric consensus statement on successful transition from paediatric to adult care for adolescents with chronic conditions.

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Around one in ten adolescents suffer from chronic conditions and disabilities, and the transition from paediatric to adult care can be particularly challenging. Unplanned transfers can complicate education, work and health and result in patients being lost to follow-up, poor treatment adherence and more frequent hospitalisation. The Adolescent Health and Medicine Working Group of the European Academy of Paediatrics has developed a consensus statement for a successful transition.**CONCLUSION:** This statement will help paediatricians, adult care specialists, policymakers and other stakeholders to handle chronic care transitions so that they meet the expectations and needs of adolescents and their families.

Epilepsy Res. 2017 Aug 3;136:103-108. doi: 10.1016/j.epilepsyres.2017.07.018. [Epub ahead of print]

Efficacy of a third or later antiepileptic drug regimen according to epilepsy syndrome among adult patients.

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OBJECTIVE: To evaluate the efficacy of third or later antiepileptic drug (AED)

regimens in adult patients with epilepsy according to epilepsy syndrome.

METHODS: The time courses of AEDs and their efficacy were evaluated in 449 adults with temporal lobe epilepsy (TLE, n=153), juvenile myoclonic epilepsy (JME, n=33), or extratemporal focal epilepsy (FE, n=263) based mainly on clinical symptoms and EEG findings. Any change in AEDs after their initiation demarcated the end of one regimen, whereas changes in dose did not. Patients were judged to be seizure-free when they had no seizures for at least 1 year with no changes in AED regimen.

RESULTS: Only 55 of 153 patients in the TLE group were free of seizures at the last visit, and the rate was significantly lower in the TLE group than the extratemporal FE group. The rate of seizure freedom with the first regimen was lower in TLE group than in the other groups, whereas the rate at the third regimen or later was significantly higher in the TLE group than the JME group. In the TLE group, a greater proportion of patients who became seizure-free with the first regimen were first treated with carbamazepine (CBZ), whereas a greater proportion of patients who became seizure-free with the fourth regimen were first treated with valproate (VPA).

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Health-related quality of life and emotional well-being after epilepsy surgery: A prospective, controlled, long-term follow-up.

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OBJECTIVE: To evaluate health-related quality of life (HRQOL) and emotional well-being in resective epilepsy surgery and nonoperated patients at long-term follow-up.

METHODS: This is a prospective cohort study where patients undergoing presurgical work-up during 1995-1998 completed the Short-Form Health Survey (SF-36) and the Hospital Anxiety and Depression scale (HAD) at baseline, and 2 and 14 years after resective surgery or presurgical evaluation (nonoperated patients). SF-36 scores were compared to a normative population. Proportions of patients reaching HRQOL changes of minimum clinically important difference (MCID) were calculated.

RESULTS: At 14-year follow-up, operated patients scored equal to or better than the normative sample on all SF-36 domains except Social Functioning and Mental Health. Physical component summary (PCS) was better and mental component summary (MCS) was worse than for the normative sample. Nonoperated patients scored worse than the normative sample on five of eight domains, and on PCS and MCS. Change in seizure status from 2 to 14 years did not affect PCS or MCS means. Improvement reaching MCID from baseline to long-term was seen in 50% (PCS) and 47% (MCS) of operated and in 33% (PCS) and 38% (MCS) of nonoperated patients. Worsening was

seen in 18% (PCS) and 22% (MCS) of operated and in 38% (PCS) and 38% (MCS) of nonoperated patients. Differences between groups were nonsignificant. HAD scores did not differ between groups, and the numbers of possible or probable cases were low. Patient satisfaction with surgery was higher in operated seizure-free patients. Only 5% of all operated patients considered surgery not to be overall beneficial.

SIGNIFICANCE: At the group level, HRQOL was stable 14 years after surgery compared to after 2 years. Social Functioning and Mental Health were still below, but other domains were similar to the normative sample. Individual patterns did not follow seizure outcome changes, indicating that multiple factors are important for long-term HRQOL.

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Follow-up study of idiopathic generalized epilepsy with associated absence seizure and myoclonic epilepsy of infancy.

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We evaluated the long-term prognosis of patients featuring the association of absences and myoclonic epilepsy of infancy. Our cohort consisted of 10 male subjects with mean age at seizure onset of 29 months. Follow-up data included seizure outcome and EEG findings. All individuals received antiepileptic drugs (AEDs) as monotherapy (6 patients) or polytherapy (4 patients) for a mean period of 24 months. Over a 30-60 month evaluation period (mean: 43 months), all patients were seizure-free. Follow-up data after withdrawal of antiepileptic therapy were obtained for a mean period of 22 months. None of the children did develop other age-related epileptic syndrome after AEDs discontinuation. Furthermore, follow-up EEG data after drugs withdrawal were normal and none of the patients showed cognitive impairment. In conclusion, we confirm that absence seizures may occur in association with myoclonic epilepsy of infancy. This condition shows excellent prognosis with either favourable neurologic development and seizure outcome in these children.

Seizure. 2017 Aug 12;51:95-101. doi: 10.1016/j.seizure.2017.08.001. [Epub ahead

of print]

Lamotrigine versus valproic acid monotherapy for generalised epilepsy: A meta-analysis of comparative studies.

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PURPOSE: The standard for generalized epilepsies (GE) monotherapy in treatment is valproic acid (VPA) and lamotrigine (LTG) has been proposed as an alternative to VPA. This study aimed to evaluate the safety and efficacy of LTG on GE seizure in comparison with VPA.

METHOD: A search was conducted based on the databases from Pubmed, Embase and the Cochran database up to February 2017. The relative risk odds ratios (ORs) and the relevant 95% confidence intervals (CI) were determined.

RESULTS: Five randomized controlled trials and four observational cohort studies involving 1732 cases were included. The results indicated that VPA was significantly superior to LTG for the outcome rate to treatment withdrawal for any reason and seizure freedom. The ORs and 95% CI of VPA versus LTG for withdrawal after 12- and 24-month treatment were 0.39(0.27, 0.56) and 0.50(0.14, 1.75), respectively, and were 3.51(2.68, 4.59) and 8.58(5.40, 13.63)for 12- and 24- month seizure free intervals, respectively. Moreover, the risk of adverse effects (OR (95%CI); 1.11(0.61-2.01)) was not significantly different between the two groups. However, the treatment withdrawal due to lack of seizure control were in the LTG group (OR (95%CI); 0.15(0.10-0.23)), while the treatment withdrawal due to intolerable side effects were in the VPA group (OR (95%CI); (1.75(1.10-2.80))).

CONCLUSIONS: The meta-analysis suggests that VPA appears to be a better choice in controlling seizure following GE. However, therapy should be switched to alternative monotherapy if an adequate trial of VPA monotherapy is not effective and intolerable, especially in young women.

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Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry.

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Vagus nerve stimulation (VNS) is an established option of adjunctive treatment for patients with drug-resistant epilepsy, however, evidence for long-term efficacy is still limited. Studies on clinical outcomes of VNS in Asia are also limited. We report the overall outcome of a national, prospective registry that included all patients implanted in Japan. The registry included patients of all ages with all seizure types who underwent VNS implantation for drug-resistant epilepsy in the first three years after approval of VNS in 2010. The registry excluded patients who were expected to benefit from resective surgery. Efficacy analysis was assessed based on the change in frequency of all seizure types and the rate of responders. Changes in cognitive, behavioural and social status, quality of life (QOL), antiepileptic drug (AED) use, and overall AED burden were analysed as other efficacy indices. A total of 385 patients were initially registered. Efficacy analyses included data from 362 patients. Age range at the time of VNS implantation was 12 months to 72 years; 21.5% of patients were under 12 years of age and 49.7% had prior epilepsy surgery. Follow-up rate was >90%, even at 36 months. Seizure control improved over time with median seizure reduction of 25.0%, 40.9%, 53.3%, 60.0%, and 66.2%, and responder rates of 38.9%, 46.8%, 55.8%, 57.7%, and 58.8% at three, six, 12, 24, and 36 months of VNS therapy, respectively. There were no substantial changes in other indices throughout the three years of the study, except for self/family-accessed QOL which improved over time. No new safety issues were identified. Although this was not a controlled comparative study, this prospective national registry of Japanese patients with drug-resistant epilepsy, with >90% follow-up rate, indicates long-term efficacy of VNS therapy which increased over time, over a period of up to three years. The limits of such trials, in terms of AED modifications and during follow-up and difficulties in seizure counting are also discussed.

Fetal Growth and Premature Delivery in Pregnant Women on Anti-epileptic Drugs.

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OBJECTIVE: To evaluate the effects of epilepsy and antiepileptic drugs (AED) use during pregnancy on fetal growth and preterm delivery.

METHODS: This study included singleton liveborns born to women enrolled in the North American Antiepileptic Drug Pregnancy Registry between 1997 and 2016. Data were collected prospectively through telephone interviews. The prevalence of preterm birth (<37 weeks) and small-for-gestational-age (SGA) among infants exposed prenatally to AED when used by women with epilepsy (WWE) or women without epilepsy (WWOE) was compared with that among infants unexposed to AEDs and born to WWOE. Multivariable log-binomial regression models were used to estimate relative risks (RR) and 95% confidence intervals (CI).

RESULTS: The study population included infants born to 6,777 AED-WWE, 696 AED-WWOE, and 486 no-AED WWOE. The risk of prematurity was 6.2% for no-AED-WWOE, 9.3% for AED-WWE (RR 1.5, 95%CI: 1.0-2.1) and 10.5% for AED-WWOE (RR 1.5: 1.0-2.4). Prenatal exposure to AED in WWE and WWOE was associated with a mean lower birth weight of 110 and 136 grams, respectively, as compared to no-AED WWOE. The prevalence of SGA was 5.0% for no-AED-WWOE, 10.9% for AED-WWE (RR 2.0: 1.3-3.0) and 11.0% for AED-WWOE (RR 1.9: 1.2-2.9). Within users of AEDs in monotherapy, the prevalence of SGA ranged from 7.3% for lamotrigine to 18.5% for topiramate.

INTERPRETATION: Women on AEDs during pregnancy, whether for epilepsy or for other neuropsychiatric indications, are at a higher risk of delivering prematurely and giving birth to SGA newborns. The risk may vary by drug. This article is protected by copyright. All rights reserved.

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Comparative effectiveness of antiepileptic drugs in patients with mesial temporal lobe epilepsy with hippocampal sclerosis.

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OBJECTIVE: Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is a common epilepsy syndrome that is often poorly controlled by antiepileptic drug (AED) treatment. Comparative AED effectiveness studies in this condition are lacking. We report retention, efficacy, and tolerability in a cohort of patients with MTLE-HS.

METHODS: Clinical data were collected from a European database of patients with epilepsy. We estimated retention, 12-month seizure freedom, and adverse drug reaction (ADR) rates for the 10 most commonly used AEDs in patients with MTLE-HS.

RESULTS: Seven hundred sixty-seven patients with a total of 3,249 AED trials were included. The highest 12-month retention rates were observed with carbamazepine (85.9%), valproate (85%), and clobazam (79%). Twelve-month seizure freedom rates varied from 1.2% for gabapentin and vigabatrin to 11% for carbamazepine. Response rates were highest for AEDs that were prescribed as initial treatment and lowest for AEDs that were used in a third or higher instance. ADRs were reported in 47.6% of patients, with the highest rates observed with oxcarbazepine (35.7%), topiramate (30.9%), and pregabalin (27.4%), and the lowest rates with clobazam (6.5%), gabapentin (8.9%), and lamotrigine (16.6%). The most commonly reported ADRs were lethargy and drowsiness, dizziness, vertigo and ataxia, and blurred vision and diplopia.

SIGNIFICANCE: Our results did not demonstrate any clear advantage of newer versus older AEDs. Our results provide useful insights into AED retention, efficacy, and ADR rates in patients with MTLE-HS.

Seizure. 2017 Aug 20;51:145-156. doi: 10.1016/j.seizure.2017.08.007. [Epub ahead of print]

Anti epileptic drug trials for patients with drug resistant idiopathic generalised epilepsy: A meta-analysis.

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PURPOSE: Determine the impact of anti-epileptic drugs (AED) for drug resistant patients with idiopathic generalised epilepsy.

METHODS: A systematic search of Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Epilepsy Group Central Specialised Register, Cochrane Central Register of controlled Trials (CENTRAL), Embase and Lensus was performed. Nine randomised controlled trials were included. All trials compared antiepileptic drugs to placebo. Outcome measures assessed were 50% or greater reduction in seizure, seizure freedom and adverse events.

RESULTS: Seven trials report a 50% or greater reduction in seizure frequency. This was statistically significant ($p < 0.00001$) with a narrow confidence interval implying that the overall this meta-analysis has reasonable power to detect an effect. It demonstrated a significant statistical difference of seizure freedom occurring in the drug treatment group compared to placebo. Adverse events were identified with each drug and are reported. There were however methodological issues with the trials included. Quality appraisal was undertaken using the risk of bias assessment from Rev Man 5.3 tool for all randomised controlled trials retrieved.

CONCLUSION: This systematic review demonstrated efficacy of adjunctive anti-epileptic drugs with regard to 50% reduction and seizure freedom. Adverse

events are identified in all of the studies in the drug treatment groups but are consistent with previous studies of these drugs. Additional adequately powered studies with long term follow up needs to be conducted to unequivocally establish the long term efficacy and tolerability of anti-epileptic drug's for patients with drug resistant idiopathic generalised epilepsy.

Neurology. 2017 Sep 19;89(12):1220-1228. doi: 10.1212/WNL.0000000000004407. Epub 2017 Aug 23.

Incidence and management of seizures after ischemic stroke: Systematic review and meta-analysis.

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OBJECTIVE: We conducted a meta-analysis of the incidence of early and late seizures following ischemic stroke as well as a systematic review of their pharmacologic treatment.

METHODS: Observational studies that reported incidence of seizures following ischemic stroke and those that reported treatment response to any particular antiepileptic drugs (AEDs) were included. Risk of bias was assessed by predefined study characteristics. Random effects meta-analysis was conducted for all studies where data were available for the incidence of early and late stroke-related seizures. Heterogeneity was measured with I(2) statistic and sensitivity analyses were performed using prespecified variables. A qualitative synthesis of studies reporting use of AEDs for stroke-related seizures was performed.

RESULTS: Forty-one studies from 10,554 articles were identified; 35 studies reported incidence of stroke-related seizures and 6 studies reported effects of specific AEDs. Most studies were of low to moderate quality. Rate of early seizures was 3.3% (95% confidence interval 2.8%-3.9%, I(2) = 92.8%), while the incidence of late seizures or epilepsy was 18 per 1,000 person-years (95% confidence interval 1.5-2.2, I(2) = 94.1%). The high degree of heterogeneity could not be explained from the sensitivity analyses. For management of stroke-related seizures, no single AED was found to be more effective over others, though newer AEDs were associated with fewer side effects.

CONCLUSIONS: The burden of stroke-related seizures and epilepsy due to ischemic stroke is substantial. Further studies are required to determine risk factors for epilepsy following ischemic stroke and optimal secondary prevention.

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Long-term risk of seizures in adult survivors of sepsis.

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OBJECTIVE: To examine the association between sepsis and the long-term risk of seizures.

METHODS: We conducted a retrospective population-based cohort study using administrative claims data from all emergency department visits and hospitalizations at nonfederal acute care hospitals in California, Florida, and New York from 2005 to 2013. Using previously validated diagnosis codes, we identified all adult patients hospitalized with sepsis. Our outcome was any emergency department visit or hospitalization for seizure. Poisson regression and demographic data were used to calculate age-, sex-, and race-standardized incidence rate ratios (IRR). To confirm our findings, we used a matched cohort of hospitalized patients without sepsis for comparison and additionally assessed claims data from a nationally representative 5% sample of Medicare beneficiaries.

RESULTS: We identified 842,735 patients with sepsis. The annual incidence of seizure was 1.29% (95% confidence interval [CI] 1.27%-1.30%) in patients with sepsis vs 0.16% (95% CI 0.16%-0.16%) in the general population (IRR 4.98; 95% CI 4.92-5.04). A secondary analysis using matched hospitalized patients confirmed these findings (IRR 4.33; 95% CI 4.13-4.55), as did a separate analysis of Medicare beneficiaries, in whom we found a similar strength of association (IRR 2.72; 95% CI 2.60-2.83), as we did in patients ≥ 65 years of age in our primary statewide data (IRR 2.83; 95% CI 2.78-2.88).

CONCLUSIONS: We found that survivors of sepsis faced a significantly higher long-term risk of seizures than both the general population and other hospitalized patients. Our findings suggest that sepsis is associated with pathways that lead to permanent neurologic sequelae.

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Potential years lost and life expectancy in adults with newly diagnosed epilepsy.

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OBJECTIVE: Studies using relative measures, such as standardized mortality ratios, have shown that patients with epilepsy have an increased mortality. Reports on more direct and absolute measure such as life expectancy are sparse. We report potential years lost and how life expectancy has changed over 40 years in a cohort of patients with newly diagnosed epilepsy.

METHODS: We analyzed life expectancy in a cohort of adult patients diagnosed with definite epilepsy between 1970 and 2010. Those with brain tumor as cause of epilepsy were excluded. By retrospective probabilistic record linkage, living or death status was derived from the national death registry. We estimated life expectancy by a Weibull regression model using gender, age at diagnosis, epilepsy etiology, and year of diagnosis as covariates at time of epilepsy diagnosis, and 5, 10, 15, and 20 years after diagnosis. Results were compared to the general population, and 95% confidence intervals are given.

RESULTS: There were 249 deaths (105 women, age at death 19.0-104.0 years) in 1,112 patients (11,978.4 person-years, 474 women, 638 men). A substantial decrease in life expectancy was observed for only a few subgroups, strongly depending on epilepsy etiology and time of diagnosis: time of life lost was highest in patients with symptomatic epilepsy diagnosed between 1970 and 1980; the impact declined with increasing time from diagnosis. Over half of the analyzed subgroups did not differ significantly from the general population. This effect was reversed in the later decades, and life expectancy was prolonged in some subgroups, reaching a maximum in those with newly diagnosed idiopathic and cryptogenic epilepsy between 2001 and 2010.

SIGNIFICANCE: Life expectancy is reduced in symptomatic epilepsies. However, in other subgroups, a prolonged life expectancy was found, which has not been reported previously. Reasons may be manifold and call for further study.

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The modified ketogenic diet for adults with refractory epilepsy: An evaluation of a set up service.

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PURPOSE: The ketogenic diet (KD) has been proven to be effective in children with refractory epilepsy and is recommended by the National Institute of Health and Care Excellence (NICE). There is no randomised control trial (RCT) evidence for the clinical or cost effectiveness of KD in adults, for whom the KD is not currently recommended. We assessed the feasibility of the modified ketogenic diet (MKD) in adults with refractory epilepsy along with the willingness of patients to participate in a future RCT.

METHODS: The service evaluation was undertaken in two parts; questionnaire and diet evaluation.

RESULTS: 102 patients completed a questionnaire, of which 51 patients were willing to try the MKD for 3 months to assess effect on seizures. Forty three patients were willing to participate in a clinical trial to investigate deliverability, efficacy and tolerability. Thirty seven of which would still be willing to participate if the trial were randomised. Of the 17 patients who commenced the diet, 9 completed the 12 week period, 7 of which stayed on the diet for the longer term. Constipation (n=6) and loose stools (n=3) were the only reported adverse effects.

CONCLUSION: Our results indicate that there is demand for a ketogenic diet service in adults. The MKD is well tolerated, feasible and financially viable to deliver to adults with epilepsy in the NHS. There is also interest in and willingness to participate in a UK based RCT that would ultimately inform decisions about commissioning appropriate services.

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Management of Epilepsy Due to Hypothalamic Hamartomas.

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A hypothalamic hamartoma consists of hyperplastic heterotopic tissue growing in a disorganized fashion. These lesions occur in about one per 50,000 to 100,000 people. Hypothalamic hamartomas can cause intrinsic epileptogenesis leading to gelastic seizures. Surrounding cortical structures may also develop secondary epileptogenesis. Persistent seizures caused by hypothalamic hamartomas can be debilitating and result in significant cognitive and behavioral impairment. Early recognition and treatment is important in controlling seizures and in preventing further cognitive deterioration. Some patients experience improved cognition and behavior following early treatment, suggesting that hypothalamic hamartomas represent a reversible epileptic encephalopathy. The outcome of epilepsy associated with these lesions has significantly evolved with the availability of new treatment techniques and an improved understanding of its pathogenesis. Increasing evidence supporting the role of hypothalamic hamartomas as a cause of gelastic seizures and secondary epileptogenesis has led to more frequent use of surgery as the definitive treatment. Several minimally invasive procedures have been devised, including neuroendoscopic approaches and different stereotactic radio and laser ablation techniques. Each of these techniques can lead to unique adverse events. We review the various classification schemes used to characterize hypothalamic hamartomas and the recommended surgical approaches for each subtype. We also review the literature for currently available treatment modalities and compare their efficacy in controlling seizures and their safety profiles.

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Rates and predictors of success and failure in repeat epilepsy surgery: A meta-analysis and systematic review.

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OBJECTIVE: Medically refractory epilepsy is a debilitating disorder that is particularly challenging to treat in patients who have already failed a surgical resection. Evidence regarding outcomes of further epilepsy surgery is limited to small case series and reviews. Therefore, our group performed the first quantitative meta-analysis of the literature from the past 30 years to assess for rates and predictors of successful reoperations.

METHODS: A PubMed search was conducted for studies reporting outcomes of repeat epilepsy surgery. Studies were excluded if they reported fewer than five eligible patients or had average follow-ups < 1 year, and patients were excluded from analysis if they received a nonresective intervention. Outcomes were stratified by each variable of interest, and quantitative meta-analysis was performed to generate odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS: Seven hundred eighty-two patients who received repeat resective epilepsy surgery from 36 studies were included. Engel I outcome was observed in 47% (n = 369) of patients. Significant predictors of seizure freedom included congruent over noncongruent electrophysiology data (OR = 3.6, 95% CI = 1.6-8.2), lesional over nonlesional epilepsy (OR = 3.2, 95% CI = 1.9-5.3), and surgical limitations over disease-related factors associated with failure of the first surgery (OR = 2.6, 95% CI = 1.3-5.3). Among patients with at least one of these predictors, seizure freedom was achieved in 58%. Conversely, the use of invasive monitoring was associated with worse outcome (OR = 0.4, 95% CI = 0.2-0.9). Temporal lobe over extratemporal/multilobe resection (OR = 1.5, 95% CI = 0.8-3.0) and abnormal over normal preoperative magnetic resonance imaging (OR = 1.9, 95% CI = 0.6-5.4) showed nonsignificant trends toward seizure freedom.

SIGNIFICANCE: This analysis supports considering further resection in patients with intractable epilepsy who continue to have debilitating seizures after an initial surgery, especially in the context of factors predictive of a favorable outcome.

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Pharmacokinetic variability of valproate in women of childbearing age.

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The purpose was to investigate pharmacokinetic variability of valproic acid (VPA) in women of childbearing age by therapeutic drug monitoring (TDM) data to elucidate the variable relationship between dose and serum concentrations with the ultimate aim of facilitating safer use of VPA. Anonymized retrospective data from the TDM database (2006-2015) at the National Center for Epilepsy in Norway were used. Trough total concentrations of VPA at assumed steady state in women aged 14-46 years were analyzed. Data from 643 nonpregnant women of childbearing age (mean age = 27 years) were included. Mean dose and serum concentration of VPA were 968 (standard deviation [SD] = 453) mg/day and 411 (SD = 138) $\mu\text{mol/L}$, respectively, and 59% used polytherapy. The pharmacokinetic variability in serum concentration/dose (C/D) ratios between women was extensive. For doses <700 mg/day (n = 202; 32%; 150-625 mg/day), mean serum concentration was 336 $\mu\text{mol/L}$ and variability in C/D ratio was 10-fold. The variability decreased with increasing dose to eightfold (≥ 700 to <1,500 mg/day, n = 358) and fourfold ($\geq 1,500$ mg/day, n = 96). This study demonstrates the extensive pharmacokinetic variability of VPA among women of childbearing age, which is most pronounced at low doses. In future studies, serum concentrations of VPA, rather than dosage,

should be used as a guide for exposure of VPA and possible risks of teratogenicity to evaluate safety aspects of VPA in women.

Seizure. 2017 Sep 14;52:63-70. doi: 10.1016/j.seizure.2017.08.014. [Epub ahead of print]

Effectiveness and tolerability of Perampanel in children, adolescents and young adults with refractory epilepsy: A UK national multicentre study.

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PURPOSE: Perampanel is one of the latest antiepileptic drugs (AEDs) approved for the treatment of focal and generalised epilepsy in individuals with epilepsy aged 12 years and older. There is sparse data on the use of Perampanel in children under 12. We conducted a study amongst paediatric neurologists in the United Kingdom to investigate its effectiveness and tolerability as an adjunctive therapy in children of all ages with refractory epilepsy.

METHODS: Data was collected via an online questionnaire sent to paediatric neurologists in the UK. Data gathered, prospective in 62 (64.5%) and retrospective in 34 (35.5%) patients, included changes in seizure frequency from baseline and unwanted effects at 3, 6 and 12 months follow-up. Only patients with a minimum follow-up of six months were included.

RESULTS: Ninety six patients (48 females) with refractory epilepsy from 11 of 29 tertiary centres were included. Median [IQR] (range) age was 14 years 11 months [12 years, 16 years 6 months] (11 months-24 years 5 months). Seventy three (76%) had focal epilepsy, sixteen (17%) generalised, and seven (7%) patients both generalised and focal epilepsy. The responder rate, $\geq 50\%$ seizure reduction from baseline, was 19% for all seizure types at both 6 and 12 months, 19% and 24% for focal seizures, and 25% and 7% for generalised seizures at these time points respectively. The retention rate was 42% at 12 months. Treatment was discontinued due to unwanted effects in 29 (36.7%) of the 79 patients with follow-up data available up to 12 months: 30% due to challenging behaviour, 14% dizziness, and 7.6% somnolence.

CONCLUSION: Perampanel was fairly effective in a heterogeneous group of 96 children and adolescents with very refractory epilepsy. The rate of adverse events leading to discontinuation was considerable in this group.

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print]

An audit of external trigeminal nerve stimulation (eTNS) in epilepsy.

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PURPOSE: External trigeminal nerve stimulation (eTNS) is a non-invasive neurostimulation treatment for drug refractory epilepsy. There is limited published data on the efficacy of eTNS and none relating to quality of life, mood or effect on sleep quality.

METHODS: We audited its use in 42 patients with drug refractory epilepsy at a tertiary centre, between 02/04/2013 and 14/08/2015. Data was collected on seizure frequency, quality of life, mood and sleep quality before and after initiating treatment.

RESULTS: 45% of patients continued to use eTNS at the end of the audit period. We observed a significant improvement in both quality of life and mood in those without intellectual disabilities. A decrease in seizures (-11.0%, min -60, max +65) was observed though this did not reach statistical significance with the relatively small numbers available for analysis.

CONCLUSION: Further controlled studies are required to confirm the efficacy of eTNS. However, as it is non-invasive, flexible and safe eTNS can be considered as an option in patients with drug refractory epilepsy.

Epileptic Disord. 2017 Oct 6. doi: 10.1684/epd.2017.0935. [Epub ahead of print]

The role of EEG in the diagnosis and classification of the epilepsy syndromes: a tool for clinical practice by the ILAE Neurophysiology Task Force (Part 1).

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The concept of epilepsy syndromes, introduced in 1989, was defined as "clusters of signs and symptoms customarily occurring together". Definition of epilepsy syndromes based on electro-clinical features facilitated clinical practice and, whenever possible, clinical research in homogeneous groups of patients with epilepsies. Progress in the fields of neuroimaging and genetics made it rapidly clear that, although crucial, the electro-clinical description of epilepsy syndromes was not sufficient to allow much needed development of targeted therapies and a better understanding of the underlying pathophysiological mechanisms of seizures. The 2017 ILAE position paper on Classification of the Epilepsies recognized that "as a critical tool for the practicing clinician, epilepsy classification must be relevant and dynamic to changes in thinking". The concept of "epilepsy syndromes" evolved, incorporating issues related to aetiologies and comorbidities. A comprehensive update (and revision where necessary) of the EEG diagnostic criteria in the light of the 2017 revised terminology and concepts was deemed necessary. The work was commissioned by the Neurophysiology Task Force of the ILAE Committee on the Diagnostic Methods. Diagnostic criteria and recording procedures were developed by group consensus, reached through an "informal", internal decision-making process. Each working group member was allocated a number of syndromes, and a standard structured template was used. International literature was extensively reviewed. We developed a simple diagnostic system that is applicable to all epilepsy syndromes which allows the physician (i) to rate the strength of EEG diagnosis (degree of diagnostic certainty) by weighting EEG findings in relation to the available clinical information or the specific clinical question, and ii) to suggest further EEG diagnostics where conclusive diagnostic evidence is lacking. We also propose a system of syndrome-specific recording protocols that, used with the relevant clinical presentation or specific clinical question, may maximize activation of epileptic discharges and ultimately help with standardization of EEG recording across departments, worldwide. Because recording methodology also depends on available resources, a two-tier system was developed to embrace clinical EEG services in resource-limited and industrialized countries. A clinical practice statement for each of the epilepsy syndromes discussed underscores the crucial role of the clinical information with regards to both the optimization of the EEG recording and mainly its meaningful interpretation. Part I covers Genetic (Idiopathic) generalized epilepsies and syndromes, Reflex epilepsies, structural and genetic focal (lobar) syndromes and Progressive Myoclonus Epilepsies [Published with educational EEG plates on www.epilepticdisorders.com].

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A randomized prospective pilot trial of Web-delivered epilepsy stigma reduction communications in young adults.

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OBJECTIVE: Epilepsy is a common neurological condition that is often associated with stigmatizing attitudes and negative stereotypes among the general public.

This randomized controlled trial (RCT) tested two new communication approaches targeting epilepsy stigma versus an education-alone approach.

METHODS: Two brief stigma-reduction videos were developed, informed by community stakeholder input; one highlighted role competency in people with epilepsy; the other highlighted social inclusion of people with epilepsy. A control video was also developed. A Web-based survey using a prospective RCT design compared effects of experimental videos and control on acceptability, perceived impact, epilepsy knowledge, and epilepsy stigma. Epilepsy knowledge and stigma were measured with the Epilepsy Knowledge Questionnaire (EKQ) and Attitudes and Beliefs about Living with Epilepsy (ABLE), respectively.

RESULTS: A total of 295 participants completed the study. Mean age was 23.1 (standard deviation = 3.27) years; 59.0% were male, and 71.4% were white.

Overall, respondents felt videos impacted their epilepsy attitudes. EKQ scores were similar across videos, with a trend for higher knowledge in experimental videos versus control ($p = 0.06$). The role competency and control videos were associated with slightly better perceived impact on attitudes. There were no differences between videos on ABLE scores ($p = 0.568$). There were subgroup differences suggesting that men, younger individuals, whites, and those with personal epilepsy experience had more stigmatizing attitudes.

SIGNIFICANCE: This RCT tested communication strategies to improve knowledge and attitudes about epilepsy. Although this initial effort will require follow-up, we have demonstrated the acceptability, feasibility, and potential of novel communication strategies to target epilepsy stigma, and a Web-based approach for assessing them.

Epilepsia. 2017 Sep 26. doi: 10.1111/epi.13913. [Epub ahead of print]

Seizures, syndromes, and etiologies in childhood epilepsy: The International

League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort.

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OBJECTIVE: The study provides updated information about the distribution of seizures, epilepsies, and etiologies of epilepsy in the general child population, and compares the old and new classification systems from the International League Against Epilepsy (ILAE).

METHODS: The study platform was the Norwegian Mother and Child Cohort Study. Cases of epilepsy were identified through registry linkages and sequential parental questionnaires. Epilepsy diagnoses were validated using a standardized protocol, and seizures, epilepsies, and etiologies were classified according to the old (ILAE 1981/1989) and new (ILAE 2017) classifications. Information was collected through medical record reviews and/or parental telephone interviews.

RESULTS: The study population included 112,744 children aged 3-13 years at the end of follow-up on December 31, 2012. Of these, there were 606 children with epilepsy (CWE). Distribution of seizure types varied by age of onset. Multiple seizure types were common with early onset. Focal epilepsies were the most common, occurring in 317 per 100,000 children in the study population and in 59% of CWE. Generalized epilepsies were found in 190 per 100,000 (35% of CWE). CWE with onset during the first 2 years of life had an even distribution of focal and generalized epilepsies, whereas focal epilepsies became dominant at later ages of onset. A definite cause of epilepsy had been demonstrated in 33% of CWE. The ILAE 1989 classification allowed for a broad syndrome category in 93% of CWE and a defined epileptic syndrome in 37%. With the ILAE 2017 classification, 41% of CWE had a defined epileptic syndrome and 63% had either a defined syndrome or structural-metabolic etiology.

SIGNIFICANCE: The distribution of seizures and epilepsies is strongly dependent on age of onset. Despite diagnostic advances, the causes of epilepsy are still unknown in two-thirds of CWE. The ILAE 2017 classifications allow for a higher precision of diagnoses, but at the expense of leaving more epilepsies classifiable only at the mode of onset level.

Epilepsy Res. 2017 Sep 19;137:56-60. doi: 10.1016/j.eplepsyres.2017.09.012. [Epub ahead of print]

Pharmacoresistance with newer anti-epileptic drugs in mesial temporal lobe epilepsy with hippocampal sclerosis.

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This study aims to evaluate the overall prognosis, prognostic factors, and efficacy of treatment in patients with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) who have access to third generation anti-epileptic drugs but not to epilepsy surgery. Eighty-five MTLE-HS patients were retrospectively placed into a seizure-free (seizure-free for >1year) or drug-resistant group, and the two groups were compared on the basis of age, sex, age at onset of seizures, duration of epilepsy, side of lesion, handedness, EEG findings, history of CNS infection, history of febrile convulsions, history of head trauma, history of cognitive impairment, family history of seizures, number of current anti-epileptic drugs (AEDs), total number of AED trials, and presence of individual AEDs. Only 24.7% of MTLE-HS patients had achieved seizure freedom for >1 year. Poor prognosis and drug-resistance were associated with younger age at onset of seizures ($p=0.002$), longer duration of epilepsy ($p=0.018$), greater number of current AEDs ($p<0.001$), and greater total number of AED trials ($p<0.001$). In addition, regimens with newer AEDs had no greater efficacy than regimens with older AEDs. Most medically managed MTLE-HS patients do not achieve seizure freedom despite multiple AED trials, and treatment with third generation AEDs should not preclude evaluation for epilepsy surgery.

Epilepsy Res. 2017 Sep 19. pii: S0920-1211(17)30408-4. doi: 10.1016/j.epilepsyres.2017.08.016. [Epub ahead of print]

Radiosurgery for epilepsy: Systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline.

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BACKGROUND: While there are many reports of radiosurgery for treatment of drug-resistant epilepsy, a literature review is lacking.

OBJECTIVE: The aim of this systematic review is to summarize current literature on the use of stereotactic radiosurgery (RS) for treatment of epilepsy.

METHODS: Literature search was performed using various combinations of the search terms "radiosurgery", "stereotactic radiosurgery", "Gamma Knife", "epilepsy" and "seizure", from 1990 until October 2015. Level of evidence was assessed according to the PRISMA guidelines.

RESULTS: Fifty-five articles fulfilled inclusion criteria. Level 2 evidence (prospective studies) was available for the clinical indications of mesial temporal lobe epilepsy (MTLE) and hypothalamic hamartoma (HH) treated by Gamma Knife (GK) RS. For remaining indications including corpus callosotomy as palliative treatment, epilepsy related to cavernous malformation and extra-temporal epilepsy, only Level 4 data was available (case report, prospective observational study, or retrospective case series). No Level 1 evidence was available.

CONCLUSION: Based on level 2 evidence, RS is an efficacious treatment to control seizures in MTLE, possibly resulting in superior neuropsychological outcomes and quality of life metrics in selected subjects compared to microsurgery. RS has a better risk-benefit ratio for small hypothalamic hamartomas compared to surgical methods. Delayed therapeutic effect resulting in ongoing seizures is associated with morbidity and mortality risk. Lack of level 1 evidence precludes the formation of guidelines at present.

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Interactions between cannabidiol and commonly used antiepileptic drugs.

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OBJECTIVE: To identify potential pharmacokinetic interactions between the pharmaceutical formulation of cannabidiol (CBD; Epidiolex) and the commonly used antiepileptic drugs (AEDs) through an open-label safety study. Serum levels were monitored to identify interactions between CBD and AEDs.

METHODS: In 39 adults and 42 children, CBD dose was started at 5 mg/kg/day and increased every 2 weeks by 5 mg/kg/day up to a maximum of 50 mg/kg/day. Serum AED levels were obtained at baseline prior to CBD initiation and at most study visits. AED doses were adjusted if it was determined that a clinical symptom or laboratory result was related to a potential interaction. The Mixed Procedure was used to determine if there was a significant change in the serum level of each of the 19 AEDs with increasing CBD dose. AEDs with interactions seen in initial analysis were plotted for mean change in serum level over time. Subanalyses were performed to determine if the frequency of sedation in participants was related to the mean serum N-desmethylclobazam level, and if aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were different in participants taking concomitant valproate.

RESULTS: Increases in topiramate, rufinamide, and N-desmethylclobazam and decrease in clobazam (all $p < 0.01$) serum levels were seen with increasing CBD dose. Increases in serum levels of zonisamide ($p = 0.02$) and eslicarbazepine ($p = 0.04$) with increasing CBD dose were seen in adults. Except for clobazam and desmethylclobazam, all noted mean level changes were within the accepted therapeutic range. Sedation was more frequent with higher N-desmethylclobazam levels in adults ($p = 0.02$), and AST/ALT levels were significantly higher in participants taking concomitant valproate ($p < 0.01$).

SIGNIFICANCE: Significantly changed serum levels of clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine were seen. Abnormal liver function test results were noted in participants taking concomitant valproate. This study emphasizes the importance of monitoring serum AED levels and LFTs during treatment with CBD.

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The retention of lacosamide in patients with epilepsy and intellectual disability in three specialised institutions.

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PURPOSE: We describe the effectiveness of lacosamide as adjunctive therapy in patients with epilepsy and an intellectual disability. This information is relevant, as few data exist pertaining to this population with a high prevalence of (intractable) epilepsy.

METHODS: We performed a retrospective study in three specialised institutions. Inclusion criteria were (1) focal onset or symptomatic generalized (2) therapy-resistant epilepsy, (3) intellectual disability and (4) residence in a care-facility for people with intellectual disabilities (PWID). The primary outcome variables were the retention rates of lacosamide, estimated through Kaplan-Meier survival analysis. Secondary outcomes were reported seizure control, side effects and clinical factors influencing discontinuation.

RESULTS: One hundred and thirty-two patients were included. The median retention time of lacosamide in our cohort was four years. The estimated one-, two- and three-year retention rates of lacosamide were 64%, 57% and 56% respectively. Severity of intellectual disability and seizure type did not influence whether lacosamide was continued. In 48.5% of patients, a reduction of seizure activity was reported. Side effects were at least part of the reason for discontinuing treatment in 26.5% of all patients. Common side effects were tiredness/somnolence (in 30.3%), aggression/agitation (24.2%), and instable gait (15.2%). Five deaths during follow-up were considered unlikely to be related to the use of lacosamide. One patient died unexpectedly within two months of treatment onset, probably this was a case of SUDEP.

CONCLUSION: These retention rates of lacosamide in PWID are similar to rates of previously registered anti-epileptic drugs in PWID. Behavioural side effects were noted in a high proportion compared to the general literature on lacosamide. Other side effects were in line with this literature. Lacosamide seems effective and safe for PWID and refractory epilepsy.

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Treatment options for posttraumatic epilepsy.

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PURPOSE OF REVIEW: Posttraumatic seizures (PTS) and posttraumatic epilepsy (PTE) are common and debilitating consequences of traumatic brain injury (TBI). Early PTS result in secondary brain injury by raising intracranial pressure and

worsening cerebral edema and metabolic crisis. PTE is a localization-related epilepsy strongly associated with TBI severity, but risk factors for PTE and epileptogenesis are incompletely understood and are active areas of research. Medical management of PTS in adults and children is reviewed. Surgical options for posttraumatic drug-resistant epilepsy are also discussed.

RECENT FINDINGS: Continuous electroencephalography is indicated for children and adults with TBI and coma because of the high incidence of nonconvulsive seizures, periodic discharges, and associated secondary brain injury in this population. Neuroinflammation is a central component of secondary brain injury and appears to play a key role in epileptogenesis. Levetiracetam is increasingly used for seizure prophylaxis in adults and children, but variability remains.

SUMMARY: PTS occur commonly after TBI and are associated with secondary brain injury and worse outcomes in adults and children. Current medical and surgical management options for PTS and PTE are reviewed.

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Epileptic headache: A rare form of painful seizure.

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PURPOSE: To describe the concept, features and mechanisms of epileptic headache (EH).

METHODS: Analysis of all published articles concerning EH and related subjects.

RESULTS: There are more than 30 published case studies of patients with headache as the only manifestation of a seizure, a condition that has been variously called "EH", "ictal epileptic headache", "hemicrania epileptica", "cephalic pain seizure". It is necessary to differentiate EH from "migralepsy" and "ictal non-epileptic headache". EH may be an isolated event or the initial phase of a seizure followed by other manifestations. An isolated EH is clinically relevant because it is often symptomatic of structural brain disease; this underlines the importance of a differential diagnosis as the head pain of EH has no specific diagnostic characteristics. The described cases indicate that the location of the foci may vary, thus suggesting the involvement of different parts of the pain network. EH is a "focal aware" seizure, but there are a few reports of cases in which it was associated with generalised epileptiform activity. A correct diagnosis of EH requires an ictal EEG recording showing epilepsy-compatible discharges that coincide with the onset and cessation of the headache. A rapid response to the acute administration of an antiepileptic drug may support the diagnosis.

CONCLUSIONS: EH is a particular type of pain seizure that has a complex pathophysiology and, when isolated, requires differential diagnostic consideration. We believe that, although it is not frequent, pain as an ictal symptom should be highlighted in the operational classification of seizure types.

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Validating epilepsy diagnoses in routinely collected data.

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PURPOSE: Anonymised, routinely-collected healthcare data is increasingly being used for epilepsy research. We validated algorithms using general practitioner (GP) primary healthcare records to identify people with epilepsy from anonymised healthcare data within the Secure Anonymised Information Linkage (SAIL) databank in Wales, UK.

METHOD: A reference population of 150 people with definite epilepsy and 150 people without epilepsy was ascertained from hospital records and linked to records contained within SAIL (containing GP records for 2.4 million people). We used three different algorithms, using combinations of GP epilepsy diagnosis and anti-epileptic drug (AED) prescription codes, to identify the reference population.

RESULTS: Combining diagnosis and AED prescription codes had a sensitivity of 84% (95% ci 77-90) and specificity of 98% (95-100) in identifying people with epilepsy; diagnosis codes alone had a sensitivity of 86% (80-91) and a specificity of 97% (92-99); and AED prescription codes alone achieved a sensitivity of 92% (70-83) and a specificity of 73% (65-80). Using AED codes only was more accurate in children achieving a sensitivity of 88% (75-95) and specificity of 98% (88-100).

CONCLUSION: GP epilepsy diagnosis and AED prescription codes can be confidently used to identify people with epilepsy using anonymised healthcare records in Wales, UK.

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Rescue Medications in Epilepsy Patients: A Family Perspective.

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PURPOSE: The aim of this study was to analyze pre-hospital seizure rescue medication (RM) use in a pediatric epilepsy population, caregiver knowledge and comfort, and prescription patterns.

METHOD: Cross-sectional observational study based on surveys to families of pediatric patients with epilepsy and based on medical chart review.

RESULTS: One hundred (92.6%) out of 114 families answered the questionnaire. Fifty-five patients were females (55%), with a median (IQR) age of 11 (6-14) years. Eighty-seven (87%) patients had RM prescribed, and 37 (42.5%) used it in the past. In univariate analysis, patients were more likely to have a RM when they had a history of SE ($p < 0.001$), or had seizures ≥ 30 seconds ($p = 0.001$). Patients were not more likely to be prescribed a RM if they were diagnosed at < 2 years of age, had ≥ 3 anti-seizure medications (ASM), had a history of seizure clusters or uncontrolled epilepsy, or were currently not on ASMs. In multivariate analysis a history of SE ($p = 0.02$) and seizure duration ≥ 30 seconds ($p = 0.04$) remained significant. Out of 91 families, 68 (74.7%) prefer a non-rectal RM; this was higher for patients with normal development, and not associated with age or sex. Fifty-three (61%) families reported that they received RM training. Ten (10.1%) parents did not know the RM name, and 31 (35.6%) did not know the administration timing. Forty-five (45%) families had a seizure action plan (SAP), and this was a predictor for knowing the RM name ($p = 0.04$), the administration timing ($p = 0.004$), availability of RM at school ($p = 0.02$), and knowing what to do if the RM fails ($p = 0.008$).

CONCLUSIONS: Most patients with epilepsy had a RM, but only 61% reported receiving training. Patients were more likely to have a RM if they had prior SE and longer seizure duration. Families with a SAP were more knowledgeable, and schools were more involved.

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Neurocysticercosis as an infectious acquired epilepsy worldwide.

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Aside from brain injury and genetic causes, there is emerging information on brain infection and inflammation as a common cause of epilepsy. Neurocysticercosis (NCC), the most common cause of epilepsy worldwide, is caused by brain cysts from the *Taenia solium* tapeworm. In this article, we provide a critical analysis of current and emerging information on the relationship between NCC infection and epilepsy occurrence. We searched PubMed and other databases for reports on the prevalence of NCC and incidence of epilepsy in certain regions worldwide. NCC is caused by brain cysts from the *T. solium* and related tapeworms. Many people with NCC infection may develop epilepsy but the rates are highly variable. MRI imaging shows many changes including localization of cysts as well as the host response to treatment. Epilepsy, in a subset of NCC patients, appears to be due to hippocampal sclerosis. Serologic and brain imaging profiles are

likely diagnostic biomarkers of NCC infection and are also used to monitor the course of treatments. Limited access to these tools is a key limitation to identify and treat NCC-related epilepsy in places with high prevalence of this parasite infestation. Overall, NCC is a common infection in many patients with epilepsy worldwide. Additional clinical and animal studies could confirm common pathology of NCC as a postinfectious epilepsy that is curable.

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Variable course of Unverricht-Lundborg disease: Early prognostic factors.

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OBJECTIVE: To explore the course of Unverricht-Lundborg disease (EPM1) and identify the risk factors for severity, we investigated the time course of symptoms and prognostic factors already detectable near to disease onset.

METHODS: We retrospectively evaluated the features of 59 Italian patients carrying the CSTB expansion mutation, and coded the information every 5 years after the disease onset in order to describe the cumulative time-dependent probability of reaching disabling myoclonus, relevant cognitive impairment, and inability to work, and evaluated the influence of early factors using the log-rank test. The risk factors were included in a Cox multivariate proportional hazards regression model.

RESULTS: Disabling myoclonus occurred an average of 32 years after disease onset, whereas cognitive impairment occurred a little later. An age at onset of less than 12 years, the severity of myoclonus at the time of first assessment, and seizure persistence more than 10 years after onset affected the timing of disabling myoclonus and cognitive decline. Most patients became unable to work years before the appearance of disabling myoclonus or cognitive decline.

CONCLUSIONS: A younger age at onset, early severe myoclonus, and seizure persistence are predictors of a more severe outcome. All of these factors may be genetically determined, but the greater hyperexcitability underlying more severe seizures and myoclonus at onset may also play a role by increasing cell damage due to reduced cystatin B activity.

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Curative and palliative MRI-guided laser ablation for drug-resistant epilepsy.

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Epilepsy is a common neurological disorder occurring in 3% of the US adult population. It is characterised by seizures resulting from aberrant hypersynchronous neural activity. Approximately one-third of newly diagnosed epilepsy cases fail to become seizure-free in response to antiseizure drugs. Optimal seizure control, in cases of drug-resistant epilepsy, often requires neurosurgical intervention targeting seizure foci, such as the temporal lobe. Advances in minimally invasive ablative surgical approaches have led to the development of MRI-guided laser interstitial thermal therapy (LITT). For refractory epilepsy, this surgical intervention offers many advantages over traditional approaches, including real-time lesion monitoring, reduced morbidity, and in some reports increased preservation of cognitive and language processes. We review the use of LITT for epileptic indications in the context of its application as a curative (seizure freedom) or palliative (seizure reduction)

measure for both lesional and non-lesional forms of epilepsy. Furthermore, we address the use of LITT for a variety of extratemporal lobe epilepsies. Finally, we describe clinical outcomes, limitations and future applications of LITT for epilepsy.

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Surgery for Drug-Resistant Epilepsy in Children.

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BACKGROUND: Neurosurgical treatment may improve seizures in children and adolescents with drug-resistant epilepsy, but additional data are needed from randomized trials.

METHODS: In this single-center trial, we randomly assigned 116 patients who were 18 years of age or younger with drug-resistant epilepsy to undergo brain surgery appropriate to the underlying cause of epilepsy along with appropriate medical therapy (surgery group, 57 patients) or to receive medical therapy alone (medical-therapy group, 59 patients). The patients in the medical-therapy group were assigned to a waiting list for surgery. The primary outcome was freedom from seizures at 12 months. Secondary outcomes were the score on the Hague Seizure Severity scale, the Binet-Kamat intelligence quotient, the social quotient on the Vineland Social Maturity Scale, and scores on the Child Behavior Checklist and the Pediatric Quality of Life Inventory.

RESULTS: At 12 months, freedom from seizures occurred in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group ($P<0.001$). Between-group differences in the change from baseline to 12 months significantly favored surgery with respect to the score on the Hague Seizure Severity scale (difference, 19.4; 95% confidence interval [CI], 15.8 to 23.1; $P<0.001$), on the Child Behavior Checklist (difference, 13.1; 95% CI, 10.7 to 15.6; $P<0.001$), on the Pediatric Quality of Life Inventory (difference, 21.9; 95% CI, 16.4 to 27.6; $P<0.001$), and on the Vineland Social Maturity Scale (difference, 4.7; 95% CI, 0.4 to 9.1; $P=0.03$), but not on the Binet-Kamat intelligence quotient (difference, 2.5; 95% CI, -0.1 to 5.1; $P=0.06$). Serious adverse events occurred in 19 patients (33%) in the surgery group, including hemiparesis in 15 (26%).

CONCLUSIONS: In this single-center trial, children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months. Surgery resulted in anticipated neurologic deficits related to the region of brain resection. (Funded by the Indian Council of Medical Research and others; Clinical Trial Registry-India number, CTRI/2010/091/000525).

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Safety at The William Quarrier Scottish Epilepsy Centre.

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PURPOSE: We examined the yield from EMFIT bed alarms and staff response time to generalised seizure in a medium term residential assessment unit for epilepsy.

METHODS: The Scottish Epilepsy Centre (SEC) has a Video Observation System (VOS) that provides continuous recording of all patient spaces (external and internal) and allows retention of clinically relevant events. A retrospective audit of daily EMFIT test records, nursing seizure record sheets (seizure type and EMFIT alert status), clinical incident reporting systems and the VOS database of retained clinical events was conducted for an 9 month period from April 1st 2016 till December 31st 2016. All generalized tonic clonic seizures (GTCS) were noted by patient, time and location and staff response time to GTCS was calculated.

RESULTS: There were 85 people admitted during the audit period who had 61 GTCS. 50 events were in bed and EMFIT alert status was recorded. On 8 occasions the EMFIT did not alert: 5 events were not of sufficient duration or frequency, in 2 the patient fell from the bed early and 1 event the alarm did not trigger. The average response time to GTCS was 23s. The longest response time was 69s (range, 0-69s, sd 15.76.).

CONCLUSIONS: The EMFIT bed alarm appears to be a valuable adjunct to safety systems. Within the novel environment of the SEC it is possible to maintain a response time to GTCS that is comparable to hospital based UK video telemetry units.

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Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors.

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OBJECTIVE: New devices are needed for monitoring seizures, especially those associated with sudden unexpected death in epilepsy (SUDEP). They must be unobtrusive and automated, and provide false alarm rates (FARs) bearable in everyday life. This study quantifies the performance of new multimodal wrist-worn convulsive seizure detectors.

METHODS: Hand-annotated video-electroencephalographic seizure events were collected from 69 patients at six clinical sites. Three different wristbands were used to record electrodermal activity (EDA) and accelerometer (ACM) signals, obtaining 5,928 h of data, including 55 convulsive epileptic seizures (six focal tonic-clonic seizures and 49 focal to bilateral tonic-clonic seizures) from 22 patients. Recordings were analyzed offline to train and test two new machine learning classifiers and a published classifier based on EDA and ACM. Moreover, wristband data were analyzed to estimate seizure-motion duration and autonomic responses.

RESULTS: The two novel classifiers consistently outperformed the previous detector. The most efficient (Classifier III) yielded sensitivity of 94.55%, and an FAR of 0.2 events/day. No nocturnal seizures were missed. Most patients had <1 false alarm every 4 days, with an FAR below their seizure frequency. When increasing the sensitivity to 100% (no missed seizures), the FAR is up to 13 times lower than with the previous detector. Furthermore, all detections occurred before the seizure ended, providing reasonable latency (median = 29.3 s, range = 14.8-151 s). Automatically estimated seizure durations were correlated with true durations, enabling reliable annotations. Finally, EDA measurements confirmed the presence of postictal autonomic dysfunction, exhibiting a significant rise in 73% of the convulsive seizures.

SIGNIFICANCE: The proposed multimodal wrist-worn convulsive seizure detectors

provide seizure counts that are more accurate than previous automated detectors and typical patient self-reports, while maintaining a tolerable FAR for ambulatory monitoring. Furthermore, the multimodal system provides an objective description of motor behavior and autonomic dysfunction, aimed at enriching seizure characterization, with potential utility for SUDEP warning.

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Identifying psychogenic seizures through comorbidities and medication history.

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OBJECTIVE: Low-cost evidence-based tools are needed to facilitate the early identification of patients with possible psychogenic nonepileptic seizures (PNES). Prior to accurate diagnosis, patients with PNES do not receive interventions that address the cause of their seizures and therefore incur high medical costs and disability due to an uncontrolled seizure disorder. Both seizures and comorbidities may contribute to this high cost.

METHODS: Based on data from 1,365 adult patients with video-electroencephalography-confirmed diagnoses from a single center, we used logistic and Poisson regression to compare the total number of comorbidities, number of medications, and presence of specific comorbidities in five mutually exclusive groups of diagnoses: epileptic seizures (ES) only, PNES only, mixed PNES and ES, physiologic nonepileptic seizurelike events, and inconclusive monitoring. To determine the diagnostic utility of comorbid diagnoses and medication history to differentiate PNES only from ES only, we used multivariate logistic regression, controlling for sex and age, trained using a retrospective database and validated using a prospective database.

RESULTS: Our model differentiated PNES only from ES only with a prospective accuracy of 78% (95% confidence interval =72-84%) and area under the curve of 79%. With a few exceptions, the number of comorbidities and medications was more

predictive than a specific comorbidity. Comorbidities associated with PNES were asthma, chronic pain, and migraines ($p < 0.01$). Comorbidities associated with ES were diabetes mellitus and nonmetastatic neoplasm ($p < 0.01$). The population-level analysis suggested that patients with mixed PNES and ES may be a population distinct from patients with either condition alone.

SIGNIFICANCE: An accurate patient-reported medical history and medication history can be useful when screening for possible PNES. Our prospectively validated and objective score may assist in the interpretation of the medication and medical history in the context of the seizure description and history.

Epilepsia. 2017 Nov;58(11):1931-1938. doi: 10.1111/epi.13893. Epub 2017 Sep 7.

Impaired bone and muscle development in young people treated with antiepileptic drugs.

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OBJECTIVE: Antiepileptic drugs (AEDs) are associated with reduced bone density, balance impairment, and increased fracture risk in adults. However, pediatric data are limited. Therefore, we aimed to examine bone, muscle, and balance outcomes in young patients taking AEDs.

METHODS: We undertook a case-control study utilizing an AED exposure-discordant matched-pair approach. Subjects were aged 5-18 years with at least 12 months of AED exposure. Pairs were twins, nontwin siblings and first cousins, sex- and age-matched (to within 2 years), allowing for greater power than with unrelated control subjects. Dual energy x-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), and muscle force/balance were tested, with questionnaires were administered for bone health and epilepsy details.

RESULTS: Twenty-three pairs were recruited, (median age 12.9 years [subjects] and 13.5 years [controls])-7 twin, 14 sibling, and 2 cousin pairs. Those taking AEDs had an increased prevalence of fractures (15 fractures in 8 subjects, compared

with 4 fractures in 3 controls, $p < 0.01$). Trabecular volumetric bone mineral density (vBMD) measured by pQCT at the 4% site (tibia) was reduced by 14% ($p = 0.03$) in subjects. Subjects exerted a decreased maximum force compared to body weight (Fmax total/g) at the tibia. There were no differences seen in either bone mineral parameters measured by DXA or balance measures.

SIGNIFICANCE: Young people taking AEDs reported more fractures and had reductions in tibial vBMD and lower limb muscle force compared to their matched controls. These findings suggest that further exploration of bone health issues of young patients on AED therapy is required. Longitudinal studies are required to confirm these changes in the muscle-bone unit and to further explore the clinical outcomes.

Neurology. 2017 Nov 8. pii: 10.1212/WNL.0000000000004740. doi: 10.1212/WNL.0000000000004740. [Epub ahead of print]

Epilepsy in multiple sclerosis: A nationwide population-based register study.

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OBJECTIVE: To determine the cumulative incidence of epilepsy in a population-based cohort of patients with multiple sclerosis (MS) and to investigate the association between epilepsy and clinical features of MS.

METHODS: All available patients in the Swedish MS register ($n = 14,545$) and 3 age- and sex-matched controls per patient randomly selected from the population register ($n = 43,635$) were included. Data on clinical features of MS were retrieved from the Swedish MS register, and data on epilepsy and death were retrieved from comprehensive patient registers.

RESULTS: The cumulative incidence of epilepsy was 3.5% (95% confidence interval [CI] 3.17-3.76) in patients with MS and 1.4% (95% CI 1.30-1.52) in controls (risk ratio 2.5, 95% CI 2.19-2.76). In a Cox proportional model, MS increased the risk of epilepsy (hazard ratio 3.2, 95% CI 2.64-3.94). Patients with relapsing-remitting MS had a cumulative incidence of epilepsy of 2.2% (95% CI 1.88-2.50), whereas patients with progressive disease had a cumulative incidence of 5.5% (95% CI 4.89-6.09). The cumulative incidence rose continuously with increasing disease duration to 5.9% (95% CI 4.90-7.20) in patients with disease duration ≥ 34 years. Patients with an Expanded Disability Status Scale (EDSS) score ≥ 7 had a cumulative incidence of epilepsy of 5.3% (95% CI 3.95-7.00). Disease duration and EDSS score were associated with epilepsy after multiple logistic regression (odds ratio [OR] 1.03, 95% CI 1.01-1.04 per year, $p = 0.001$; and OR 1.2, 95% CI 1.09-1.26 per EDSS step, $p < 0.0001$).

CONCLUSIONS: Epilepsy is more common among patients with MS than in the general population, and a diagnosis of MS increases the risk of epilepsy. Our data

suggest a direct link between severity of MS and epilepsy.

Seizure. 2017 Nov 7;53:55-61. doi: 10.1016/j.seizure.2017.11.003. [Epub ahead of print]

Telephonic review for outpatients with epilepsy-A prospective randomized, parallel group study.

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PURPOSE: Our objective was to assess how telephonic review of outpatients with stable epilepsy compared with conventional face-to-face clinic management.

METHODS: We constructed a randomized parallel group study of suitable patients attending our Epilepsy Clinic and compared telephonic review with conventional clinic visit based management. Primary outcomes were the percentage of patients with breakthrough seizures and total number of breakthrough seizures. We also compared cost, patient satisfaction and numbers defaulting.

RESULTS: A total of 465 patients were randomized and 429 were included in the final analysis. There was no significant difference in breakthrough seizures between the two groups. Mean time spent in the consultation was 10min in the telephone group (FT) and 22h in the face-to-face group (FC) and cost was INR 865 more expensive on an average in the FC group. Satisfaction was over 90% in the FT group. Significantly more people in the FC group were lost to follow-up.

CONCLUSION: This study provides Class I evidence that the number of stable epilepsy patients who have breakthrough seizures and the total number of breakthrough seizures remain the same irrespective of whether patients are reviewed telephonically or face-to-face in the clinic. Clinicians managing epilepsy patients should consider using telephonic review for selected patients. Telephonic reviews have the potential of effectively reducing the secondary treatment gap in millions of patients who do not have easy access to doctors.

Seizure. 2017 Nov 20;54:1-6. doi: 10.1016/j.seizure.2017.11.011. [Epub ahead of print]

Visual field defects after temporal lobe resection for epilepsy.

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PURPOSE: To determine visual field defects (VFDs) using methods of varying complexity and compare results with subjective symptoms in a population of newly operated temporal lobe epilepsy patients.

METHODS: Forty patients were included in the study. Two patients failed to perform VFD testing. Humphrey Field Analyzer (HFA) perimetry was used as the gold standard test to detect VFDs. All patients performed a web-based visual field test called Damato Multifixation Campimetry Online (DMCO). A bedside confrontation visual field examination ad modum Donders was extracted from the medical records in 27/38 patients. All participants had a consultation by an ophthalmologist. A questionnaire described the subjective complaints.

RESULTS: A VFD in the upper quadrant was demonstrated with HFA in 29 (76%) of the 38 patients after surgery. In 27 patients tested ad modum Donders, the sensitivity of detecting a VFD was 13%. Eight patients (21%) had a severe VFD similar to a quadrant anopia, thus, questioning their permission to drive a car.

In this group of patients, a VFD was demonstrated in one of five (sensitivity=20%) ad modum Donders and in seven of eight (sensitivity=88%) with DMCO. Subjective symptoms were only reported by 28% of the patients with a VFD and in two of eight (sensitivity=25%) with a severe VFD. Most patients (86%) considered VFD information mandatory.

CONCLUSION: VFD continue to be a frequent adverse event after epilepsy surgery in the medial temporal lobe and may affect the permission to drive a car in at least one in five patients. Subjective symptoms and bedside visual field testing ad modum Donders are not sensitive to detect even a severe VFD. Newly developed web-based visual field test methods appear sensitive to detect a severe VFD but perimetry remains the golden standard for determining if visual standards for driving is fulfilled. Patients consider VFD information as mandatory.

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Deep brain stimulation for drug-resistant epilepsy.

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OBJECTIVES: To review clinical evidence on the antiepileptic effects of deep brain stimulation (DBS) for drug-resistant epilepsy, its safety, and the factors influencing individual outcomes.

METHODS: A comprehensive search of the medical literature (PubMed, Medline) was conducted to identify relevant articles investigating DBS therapy for drug-resistant epilepsy. Reference lists of these articles were used to source further articles.

RESULTS: Stimulation of the anterior nucleus of the thalamus (ANT) and hippocampus (HC) has been shown to decrease the frequency of refractory seizures. Half of all patients from clinical studies experienced a 46%-90% seizure reduction with ANT-DBS, and a 48%-95% seizure reduction with HC-DBS. The efficacy of stimulating other targets remains inconclusive due to lack of evidence.

Approximately three-fourths of patients receiving ANT, HC, or centromedian nucleus of the thalamus (CMT) stimulation are responders-experiencing a seizure reduction of at least 50%. The time course of clinical benefit varies dramatically, with both an initial lesional effect and ongoing stimulation effect at play. Improved quality of life and changes to cognition or mood may also occur. Side effects are similar in nature to those reported from DBS therapy for movement disorders. Several factors are potentially associated with stimulation efficacy, including an absence of structural abnormality on imaging for ANT and HC stimulation, and electrode position relative to the target. Certain seizure types or syndromes may respond more favorably to specific targets, including ANT stimulation for deep temporal or limbic seizures, and CMT stimulation for generalized seizures and Lennox-Gastaut syndrome.

SIGNIFICANCE: We have identified several patient, disease, and stimulation factors that potentially predict seizure outcome following DBS. More large-scale clinical trials are needed to explore different stimulation parameters, reevaluate the indications for DBS, and identify robust predictors of patient response.

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Cannabinoids for epilepsy: What do we know and where do we go?

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Over the past decade there has been an increasing interest in using cannabinoids to treat a range of epilepsy syndromes following reports of some remarkable responses in individual patients. The situation is complicated by the fact that these agents do not appear to work via their attachment to endogenous cannabinoid receptors. Their pharmacokinetics are complex, and bioavailability is variable,

resulting in difficulty in developing a suitable formulation for oral delivery. Drug interactions also represent another complication in their everyday use. Nevertheless, recent randomized, placebo-controlled trials with cannabidiol support its efficacy in Dravet and Lennox-Gastaut syndromes. Further placebo-controlled studies are underway in adults with focal epilepsy using cannabidivarin. The many unanswered questions in the use of cannabinoids to treat epileptic seizures are briefly summarized in the conclusion.

Epilepsy Res. 2017 Nov 28;139:73-79. doi: 10.1016/j.eplepsyres.2017.11.015. [Epub ahead of print]

The new definition and classification of seizures and epilepsy.

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This review discusses the updated classifications of seizures and the epilepsies, which were recently published by the International League Against Epilepsy (ILAE). While it is always a challenge to learn a new classification system, particularly one that has remained essentially unchanged for over three decades, these new classifications allow for the inclusion of some previously unclassifiable seizure types and utilize more intuitive terminology. In this review, we specifically discuss the use of these new classifications for patients, clinicians, and researchers.

Epilepsia. 2017 Dec;58(12):2164-2171. doi: 10.1111/epi.13934. Epub 2017 Nov 3.

Potentially high-risk cardiac arrhythmias with focal to bilateral tonic-clonic seizures and generalized tonic-clonic seizures are associated with the duration of periictal hypoxemia.

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OBJECTIVE: To investigate potentially high-risk cardiac arrhythmias (PHAs)

following focal to bilateral tonic-clonic seizures (FBTCSs) and generalized tonic-clonic seizures (GTCSs) and to study the association of PHAs with seizure characteristics and the severity of associated ictal respiratory dysfunction.

METHODS: Electrocardiographic (EKG) and pulse oximetry (SpO₂) data were recorded concurrently with video-electroencephalographic telemetry in the epilepsy monitoring unit (EMU). One minute of preictal EKG, the ictal EKG, and 2 min of ictal/postictal data were reviewed for each seizure. Nonsustained ventricular tachycardia, bradyarrhythmia, and/or sinus pauses were considered as PHAs. FBTCSs/GTCSs with PHAs were compared to those that had only ictal sinus tachycardia.

RESULTS: Data from 69 patients with 182 FBTCSs/GTCSs with usable SpO₂ and EKG recordings were available. There were 10 FBTCSs/GTCSs in 10 patients with a PHA. The presence of PHAs was not associated with seizure duration or SpO₂ nadir. FBTCSs/GTCSs with a PHA were significantly associated with the duration of oxygen desaturation < 90% when compared with FBTCSs/GTCSs with only sinus tachycardia (Mann-Whitney, $p = 0.042$). Desaturation duration of <100 s was not significantly associated with occurrence of PHAs ($p = 0.110$) when compared with seizures that had only sinus tachycardia. The odds ratio for occurrence of PHA was 7.86 for desaturation durations ≥ 125 s versus desaturations < 125 s ($p = 0.005$). The odds ratio increased to 13.09 for desaturation durations ≥ 150 s ($p < 0.001$). Preictal and ictal/postictal arrhythmias occurred with focal seizures that did not progress to FBTCSs. Four patients with focal seizures had ictal/postictal PHAs without preictal PHAs. Two of these patients had evidence for prior cardiac disturbance.

SIGNIFICANCE: PHAs following a single FBTCS/GTCS in the EMU are significantly associated with the duration of ictal/postictal hypoxemia. It is possible that FBTCS/GTCS-associated hypoxemia may trigger fatal cardiac arrhythmias in a subset of susceptible patients dying of sudden unexpected death in epilepsy.

J Neurol Neurosurg Psychiatry. 2017 Dec 9. pii: jnnp-2017-316578. doi: 10.1136/jnnp-2017-316578. [Epub ahead of print]

Auras and the risk of seizures with impaired consciousness following epilepsy surgery: implications for driving.

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OBJECTIVE: To calculate the chance of a seizure in the next year (COSY) for seizures with impaired awareness in those experiencing auras only, those with no seizures and those with continuing seizures. Epilepsy surgery is an effective treatment for refractory focal epilepsy. Driving is an important factor affecting quality of life. In the UK, driving is not permitted if focal seizures with no impairment of awareness (auras, simple partial seizures) continue, if there is a prior history of seizures with impaired awareness, as will invariably be the case

in those having epilepsy surgery. Current UK driving regulations allow driving if COSY is less than 20%.

METHOD: We calculated COSY in 819 epilepsy surgery patients with up to 25 years follow-up. Each patient year was graded on the The International League against Epilepsy surgery outcome scale.

RESULTS: Patients who were entirely seizure-free for 1, 2 and 3 years had COSY of 4.9%, 3.5% and 2.4% respectively. Patients with only auras within the last 1, 2 or 3 years had a COSY of 11.3%, 9.2% and 7.8% respectively.

CONCLUSIONS: Individuals with auras only after epilepsy surgery had a higher COSY than those who were seizure-free. If a COSY of below 20% is regarded as an acceptable risk, it may be suggested that those with auras only in a given year be allowed to drive. The relative risk of these patients causing accidents is lower than population groups such as those aged <25 or >75 years, who are permitted to drive.

Curr Opin Neurol. 2017 Dec 22. doi: 10.1097/WCO.0000000000000528. [Epub ahead of print]

The current place of epilepsy surgery.

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PURPOSE OF REVIEW: Three randomized controlled trials demonstrate that surgical treatment is safe and effective for drug-resistant epilepsy (DRE), yet fewer than 1% of patients are referred for surgery. This is a review of recent trends in surgical referral for DRE, and advances in the field. Reasons for continued underutilization are discussed.

RECENT FINDINGS: Recent series indicate no increase in surgical referral for DRE over the past two decades. One study suggests that decreased referrals to major epilepsy centers can be accounted for by increased referrals to low-volume nonacademic hospitals where results are poorer, and complication rates higher. The increasing ability of high-resolution MRI to identify small neocortical lesions and an increase in pediatric surgeries, in part, explain a relative greater decrease in temporal lobe surgeries. Misconceptions continue to restrict referral. Consequently, advocacy for referral of all patients with DRE to epilepsy centers that offer specialized diagnosis and other alternative treatments, as well as psychosocial support, is recommended. Recent advances will continue to improve the safety and efficacy of surgical treatment and expand the types of patients who benefit from surgical intervention.

SUMMARY: Surgical treatment for epilepsy remains underutilized, in part because of persistent misconceptions. Rather than promote referral for surgery, it would be more appropriate to advocate that all patients with DRE deserve a consultation at a full-service epilepsy center that offers many options for eliminating or reducing disability.

Curr Opin Neurol. 2017 Dec 18. doi: 10.1097/WCO.0000000000000529. [Epub ahead of print]

The first seizure as an indicator of epilepsy.

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PURPOSE OF REVIEW: Optimal treatment of a possible first seizure depends on the determination if the paroxysmal event was an epileptic seizure and was on an accurate assessment of the recurrence risk. This review summarizes evidence from the last 5 years addressing the following questions: Is it an epileptic seizure?

Is it a first seizure? When does a first seizure indicate epilepsy?

RECENT FINDINGS: The acts of taking and interpreting the history from patients and witnesses continue to be the most important tools in the diagnosis of first seizures. Assessment tools based on factual questions and the observation of patients' conversational behaviour can contribute to the differentiation of patients with epileptic seizures from those who have experienced other types of transient loss of consciousness (TLOC). At present, only about 40% of patients are seen after their very first seizure. Tests have a limited role in the initial diagnosis of a seizure but help to determine the recurrence risk based on the cause. A remote symptomatic cause and detection of epileptiform discharges are associated with a recurrence risk of at least 60% and allow a diagnosis of epilepsy after a first seizure. The risk of recurrence after an acute symptomatic first seizure is well below 60%.

SUMMARY: Expert history-taking continues to be the most important tool in the diagnosis of a first seizure. Cause is the most important determinant of the recurrence risk. Unfortunately, there is currently no formula enabling a precise calculation of an individualized recurrence risk.

J Neurol Neurosurg Psychiatry. 2017 Dec 23. pii: jnnp-2017-317102. doi: 10.1136/jnnp-2017-317102. [Epub ahead of print]

Systematic review of structural and functional brain alterations in psychosis of epilepsy.

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This systematic review critically assesses structural and functional neuroimaging studies of psychosis of epilepsy (POE). We integrate findings from 18 studies of adults with POE to examine the prevailing view that there is a specific relationship between temporal lobe epilepsy (TLE) and POE, and that mesial temporal lobe pathology is a biomarker for POE. Our results show: (1) conflicting evidence of volumetric change in the hippocampus and amygdala; (2) distributed structural pathology beyond the mesial temporal lobe; and (3) changes in frontotemporal functional network activation. These results provide strong evidence for a revised conceptualisation of POE as disorder of brain networks, and highlight that abnormalities in mesial temporal structures alone are unlikely to account for its neuropathogenesis. Understanding POE as a disease of brain networks has important implications for neuroimaging research and clinical practice. Specifically, we suggest that future neuroimaging studies of POE target structural and functional networks, and that practitioners are vigilant for psychotic symptoms in all epilepsies, not just TLE.

Brain Dev. 2017 Dec 30. pii: S0387-7604(17)30311-X. doi: 10.1016/j.braindev.2017.12.005. [Epub ahead of print]

Hydrocephalus in pyridoxine-dependent epilepsy: New case and literature review.

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INTRODUCTION: Pyridoxine-dependent epilepsy (PDE) is a rare disorder of the lysine metabolism, characterized by a pharmacoresistant epileptic encephalopathy that usually begins in the neonatal period. However, its phenotypic spectrum is wide and not limited to seizures. We report a new case of PDE who developed hydrocephalus, along with an exhaustive review of the literature.

CASE REPORT: Our patient presented with seizures at 13 h of life. Antiepileptic drugs, vitamins and cofactors were required to achieve seizure control.

Laboratory tests were congruent with PDE. She remained seizure-free until age five months, when seizures reappeared in the context of increasing head size and irritability. A cranial ultrasound showed hydrocephalus, for which she underwent ventriculoperitoneal shunting.

DISCUSSION: Seven other patients with same features have been previously reported. Seizure onset occurred within the first 7 days in all patients. Most of the children developed hydrocephalus at 6-7 months of age. In 4 out of 7 a genetic mutation was identified, despite the accurate etiology of hydrocephalus was unknown in most of them. The case we report behaved similarly to the others previously described. We postulate that the pathogenesis of this complication could be related to the high expression of antiqutin in choroid plexus epithelium, where the cerebrospinal fluid is produced.

CONCLUSIONS: patients with PDE should be closely monitored, since they may present severe complications. We highlight the development of hydrocephalus, an uncommon but potentially life-threatening problem reported in 8 patients up to present time.

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Epilepsy in an elderly population: Classification, etiology and drug resistance.

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PURPOSE: To characterize epilepsy in an elderly population and describe the prevalence of drug resistant epilepsy (DRE) using recently validated International League Against Epilepsy (ILAE) criteria.

METHODS: Using a case-control design, 72 patients aged 60 years and older (cases) and 223 patients under age 60 (controls) were identified from the Saskatchewan Epilepsy Program database. Patients' charts were retrospectively reviewed. Bivariate and multiple logistic regression analyses were performed to identify variables that were associated with epilepsy in elderly patients.

RESULTS: Forty-seven elderly patients (65%) had focal epilepsy, while 9 (13%) had generalized epilepsy. The most common etiology in elderly patients with epilepsy was unknown in 30 (48%) patients. Other identified etiologies included brain tumors in 14 (19.4%), genetic in 6 (8%), degenerative disease in 4 (5%), stroke in 6 (8%) and head injury in 3 (4%). Significantly fewer elderly patients met criteria for DRE compared to non-elderly patients (26% vs. 51%, $p = 0.001$). In the multiple logistic regression analysis, elderly patients with epilepsy were more likely to have the presence of stroke, psychiatric comorbidity and to be on monotherapy.

CONCLUSION: In our sample, elderly patients with epilepsy were more likely to have seizures resulting from brain tumors and stroke, and less likely to have DRE than non-elderly patients. These unique features of elderly patients strongly suggest that clinical practice guidelines are needed to facilitate the highest quality of care in elderly patients with epilepsy.

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Online patient information on Vagus Nerve Stimulation: How reliable is it for facilitating shared decision making?

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PURPOSE: This study evaluates the quality of information available on the internet for carers of children with epilepsy considering treatment with Vagus Nerve Stimulation (VNS).

METHODS: Selected key phrases were entered into two popular search engines (Google™, Yahoo™). These phrases were: "Vagus nerve stimulator", alone and in combination with "childhood epilepsy", "paediatric epilepsy" and "epilepsy in childhood"; "VNS", and "VNS epilepsy". The first 50 hits per search were then screened. Of 600 identified sites, duplicated (262), irrelevant (230) and inaccessible (15) results were excluded. 93 websites were identified for evaluation using the DISCERN instrument, an online validation tool for patient information websites.

RESULTS: The mean DISCERN score of all analysed websites was 39/80 (49%; SD 13.5). This equates to Fair to borderline Poor global quality, (Excellent=80-63; Good=62-51; Fair=50-39; Poor=38-27; Very poor=26-15). None of the analysed sites obtained an Excellent quality rating. 13% (12) obtained a Good score, 40% (37) obtained an Average score, 35% (33) obtained a Poor score, and 12% (11) obtained a Very poor score. The cohort of websites scored particularly poorly on assessment of whether reliable, holistic information was presented, for instance provision of reliable sources, (28%, SD 18) and discussion of alternative treatments, (30%, SD 14).

CONCLUSION: To facilitate patient-centred shared decision-making, high quality information needs to be available for patients and families considering VNS. This study identifies that such information is difficult to locate on the internet. There is a need to develop focussed and reliable online patient resources for VNS.

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Perampanel in the general population and in people with intellectual disability: Differing responses.

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PURPOSE: There is a shortfall of suitably powered studies to provide evidence for safe prescribing of AEDs to people with Intellectual Disability (ID). We report clinically useful information on differences in response to Perampanel (PER) adjunctive treatment for refractory epilepsy between ID sub-groups and general population from the UK Ep-ID Research Register.

METHOD: Pooled retrospective case notes data of consented people with epilepsy (PWE) prescribed PER from 6 UK centres was classified as per WHO guidance into groups of moderate -profound ID, mild ID and General population. Demographics, concomitant AEDs, starting and maximum dosage, exposure length, adverse effects, dropout rates, seizure type and frequency were collected. Group differences were reported as odds ratios estimated from univariable logistic regression models.

RESULTS: Of the 144 PWE (General population 71, Mild ID 48, Moderate to profound ID 48) examined the association between withdrawal and ID type was marginally statistically significant ($p=0.07$). Moderate to profound ID PWE were less likely to come off PER compared to mild ID (OR=0.19, CI=0.04-0.92, $p=0.04$). Differences in mental health side effects by groups was marginally statistically significant ($p=0.06$). Over 50% seizure improvement was seen in 11% of General population, 24% mild ID and 26% Moderate to profound ID.

CONCLUSIONS: PER seems safe in PWE with ID. It is better tolerated by PWE with Moderate to profound ID than PWE with higher functioning. Caution is advised when history of mental health problems is present. The standardised approach of the Ep-ID register UK used confirms that responses to AEDs by different ID groups vary between themselves and General population.

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Cochrane systematic review and meta-analysis of the impact of psychological treatments for people with epilepsy on health-related quality of life.

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OBJECTIVE: Given the significant impact epilepsy can have on health-related quality of life (HRQoL) of individuals with this condition and their families, there is great clinical interest in evidence-based psychological treatments aimed at enhancing well-being in people with epilepsy (PWE). An evaluation of the current evidence is needed to assess the effects of psychological treatments for PWE on HRQoL outcomes to inform future therapeutic recommendations and research designs.

METHODS: The operational definition of psychological treatments included a broad range of interventions that use psychological or behavioral techniques designed to improve HRQoL, psychiatric comorbidities, and seizure frequency and severity for adults and children with epilepsy. A systematic literature search was conducted in line with Cochrane criteria for randomized controlled trials (RCTs) and quasi-RCTs investigating psychological treatments and using HRQoL outcome measures as primary or secondary outcome measures. Standard methodological procedures required by the Cochrane Collaboration were used for data collection and analysis.

RESULTS: Twenty-four completed RCTs were included in this review (2439 participants). Based on satisfactory methodological homogeneity, data from 9 studies (468 participants) providing Quality of Life in Epilepsy-31 (QOLIE-31) outcomes were pooled for meta-analyses, showing significant mean changes for QOLIE-31 total score and 6 subscales. The significant mean changes of QOLIE-31 total score (mean improvement of 5.68 points; 95% confidence interval = 3.11-8.24, $P < .0001$) and 3 subscales (emotional well-being, energy/fatigue, overall quality of life [QoL]) exceeded the threshold of minimally important change, indicating a clinically meaningful postintervention improvement of QoL. Overall, the meta-analysis quality of evidence was characterized as "moderate" due to the risk of bias present in 8 of the 9 included studies (Handbook for Systematic Reviews of Interventions, Version 5.1.0, 2011, Chapters 8 and 12). A narrative synthesis was conducted for all trials and outcomes that were not entered in the meta-analysis.

SIGNIFICANCE: These results provide moderate-quality evidence that psychological treatments for adults with epilepsy may enhance HRQoL in people with epilepsy.

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Return to driving after a diagnosis of epilepsy: A prospective registry study.

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OBJECTIVE: To determine the frequency and predictors of return to driving within 1 year after a diagnosis of epilepsy.

METHODS: SEISMIC (the Sydney Epilepsy Incidence Study to Measure Illness Consequences) was a prospective, multicenter, community-wide study of people of all ages with newly diagnosed epilepsy in Sydney, Australia. Demographic, socioeconomic, and clinical characteristics and driving status were obtained as soon as possible after baseline registration with a diagnosis of epilepsy.

Multivariate logistic regression was used to determine predictors of return to driving at 12-month follow-up.

RESULTS: Among 181 (76%) adult participants (≥ 18 years old) who reported driving before an epilepsy diagnosis, 152 provided information on driving at 12 months, of whom 118 (78%) had returned to driving. Driving for reasons of getting to work or place of education (odds ratio [OR] = 4.70, 95% confidence intervals [CI] = 1.87-11.86), no seizure recurrence (OR = 5.15, 95% CI = 2.07-12.82), and being on no or a single antiepileptic drug (OR = 4.54, 95% CI = 1.45-14.22) were associated with return to driving (C statistic = 0.79). More than half of participants with recurrent seizures were driving at follow-up.

SIGNIFICANCE: Early return to driving after a diagnosis of epilepsy is related to work/social imperatives and control of seizures, but many people with recurrent seizures continue to drive. Further efforts are required to implement driving restriction policies and to provide transport options for people with epilepsy.

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Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study.

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Progressive functional decline in the epilepsies is largely unexplained. We formed the ENIGMA-Epilepsy consortium to understand factors that influence brain measures in epilepsy, pooling data from 24 research centres in 14 countries across Europe, North and South America, Asia, and Australia. Structural brain measures were extracted from MRI brain scans across 2149 individuals with epilepsy, divided into four epilepsy subgroups including idiopathic generalized epilepsies ($n = 367$), mesial temporal lobe epilepsies with hippocampal sclerosis (MTLE; left, $n = 415$; right, $n = 339$), and all other epilepsies in aggregate ($n = 1026$), and compared to 1727 matched healthy controls. We ranked brain structures in order of greatest differences between patients and controls, by meta-analysing effect sizes across 16 subcortical and 68 cortical brain regions. We also tested effects of duration of disease, age at onset, and age-by-diagnosis interactions on structural measures. We observed widespread patterns of altered subcortical volume and reduced cortical grey matter thickness. Compared to controls, all epilepsy groups showed lower volume in the right thalamus (Cohen's $d = -0.24$ to -0.73 ; $P < 1.49 \times 10^{-4}$), and lower thickness in the precentral gyri bilaterally ($d = -0.34$ to -0.52 ; $P < 4.31 \times 10^{-6}$). Both MTLE subgroups showed profound volume reduction in the ipsilateral hippocampus ($d = -1.73$ to -1.91 , $P < 1.4 \times 10^{-19}$), and lower thickness in extrahippocampal cortical regions, including the precentral and paracentral gyri, compared to controls ($d = -0.36$ to -0.52 ; $P <$

1.49×10^{-4}). Thickness differences of the ipsilateral temporopolar, parahippocampal, entorhinal, and fusiform gyri, contralateral pars triangularis, and bilateral precuneus, superior frontal and caudal middle frontal gyri were observed in left, but not right, MTLE ($d = -0.29$ to -0.54 ; $P < 1.49 \times 10^{-4}$). Contrastingly, thickness differences of the ipsilateral pars opercularis, and contralateral transverse temporal gyrus, were observed in right, but not left, MTLE ($d = -0.27$ to -0.51 ; $P < 1.49 \times 10^{-4}$). Lower subcortical volume and cortical thickness associated with a longer duration of epilepsy in the all-epilepsies, all-other-epilepsies, and right MTLE groups ($\beta, b < -0.0018$; $P < 1.49 \times 10^{-4}$). In the largest neuroimaging study of epilepsy to date, we provide information on the common epilepsies that could not be realistically acquired in any other way. Our study provides a robust ranking of brain measures that can be further targeted for study in genetic and neuropathological studies. This worldwide initiative identifies patterns of shared grey matter reduction across epilepsy syndromes, and distinctive abnormalities between epilepsy syndromes, which inform our understanding of epilepsy as a network disorder, and indicate that certain epilepsy syndromes involve more widespread structural compromise than previously assumed.

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Epidemiologist's view: Addressing the epilepsy surgery treatment gap with minimally-invasive techniques.

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Despite the fact that epilepsy surgery is both safe and effective, a considerable "surgical treatment gap" remains in that most persons who are eligible for surgery do not receive it. It has been argued that epilepsy surgery is one of the most underutilized of all accepted medical treatments in the world. In this article, we review the epidemiology of the epilepsy surgery treatment gap, and consider the role minimally-invasive epilepsy surgery may play in reducing this gap.

ENDS

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Comparison of brand versus generic antiepileptic drug adverse event reporting rates in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).

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OBJECTIVE: Despite the cost saving role of generic anti-epileptic drugs (AEDs), debate exists as to whether generic substitution of branded AEDs may lead to therapeutic failure and increased toxicity. This study compared adverse event (AE) reporting rates for brand vs. authorized generic (AG) vs. generic AEDs. Since AGs are pharmaceutically identical to brand but perceived as generics, the generic vs. AG comparison minimized potential bias against generics.

METHODS: Events reported to the U.S. Food and Drug Administration Adverse Event Reporting System between January 2004 to March 2015 with lamotrigine, carbamazepine, and oxcarbazepine listed as primary or secondary suspect were classified as brand, generic, or AG based on the manufacturer. Disproportionality analyses using the reporting odds ratio (ROR) assessed the relative rate of reporting of labeled AEs compared to reporting these events with all other drugs. The Breslow-Day statistic compared RORs across brand, AG, and other generics using a Bonferroni-corrected $P < 0.01$.

RESULTS: A total of 27,150 events with lamotrigine, 13,950 events with carbamazepine, and 5077 events with oxcarbazepine were reported, with generics accounting for 27%, 41%, and 32% of reports, respectively. Although RORs for the

majority of known AEs were different between brand and generics for all three drugs of interest (Breslow-Day $P < 0.001$), RORs generally were similar for AG and generic comparisons. Generic lamotrigine and carbamazepine were more commonly involved in reports of suicide or suicidal ideation compared with the respective AGs based on a multiple comparison-adjusted $P < 0.01$.

SIGNIFICANCE: Similar AED reporting rates were observed for the AG and generic comparisons for most outcomes and drugs, suggesting that brands and generics have similar reporting rates after accounting for generic perception biases.

Disproportional suicide reporting was observed for generics compared with AGs and brand, although this finding needs further study.

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Impact of generic substitution on levetiracetam serum concentration-A prospective study in an outpatient setting.

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BACKGROUND: Switching patients from a branded antiepileptic drug (AED) to a generic is often challenging. Several studies have shown that considerable proportions of patients report deteriorated seizure control or increased adverse effects, enforcing a switchback to the original drug. Since tolerability and seizure control usually correlate with AED serum concentrations, we examined the fluctuation of levetiracetam (LEV) serum concentrations in patients with epilepsy before and after generic substitution.

METHODS: This was an 18-week, naturalistic, open, prospective, two-center study. After a baseline period of 10 weeks, 33 outpatients on stable treatment with branded LEV (Keppra®) either continued with this product or were switched overnight to a generic LEV preparation (1A Pharma) for an eight-week study

period. Throughout the study, patients were monitored with bi-weekly LEV serum concentration measurements and seizure diaries.

RESULTS: 16 out of 33 patients were switched to a generic LEV product. No switchbacks were seen. LEV dose, LEV serum concentrations, fluctuation index and concentration/dose-ratio (C/D-ratio) were not significantly different within-group (baseline vs. study period) or between-group. Large within-subject variability in serum concentrations was seen in both groups. None of the patients that were seizure-free before inclusion experienced seizures while on the generic LEV product.

CONCLUSIONS: Our results show equal fluctuation of LEV serum concentrations with branded LEV and the generic LEV. Most importantly, within-subject variability was much larger than the small, non-significant differences between brands.

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Risk for injuries and accidents in epilepsy: A prospective population-based cohort study.

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OBJECTIVE: To study the risk for injuries/accidents in people with newly diagnosed epileptic seizures in relation to comorbidities.

METHODS: Between September 1, 2001, and August 31, 2008, individuals in northern Stockholm with incident unprovoked seizures (epilepsy; n = 2,130) were included in a registry. For every epilepsy patient, 8 individuals matched for sex and inclusion year (n = 16,992) were randomly selected as references from the population of the catchment area. Occurrence of injuries/accidents was monitored through the national patient and cause of death registers until December 31, 2013. These registers also provided information on comorbidities (e.g., brain tumor, stroke, psychiatric disease, diabetes mellitus).

RESULTS: Injury/accident was demonstrated in 1,033 epilepsy cases and 6,202 references (hazard ratio [HR] 1.71, 95% confidence interval 1.60-1.83). The excess risk was seen mainly during the first 2 years after diagnosis. Sex and educational status had no significant effect on HR. The risk was normal in children but increased in adults. Highest HR was seen for drowning, poisoning, adverse effect of medication, and severe traumatic brain injury. Compared to references without comorbidities, HR was 1.17 (1.07-1.28) in epilepsy without comorbidities, 4.52 (4.18-4.88) in references with comorbidities, and 7.15 (6.49-7.87) in epilepsy with comorbidities.

CONCLUSION: Presence of comorbidities should be considered when counseling patients with newly diagnosed epilepsy concerning risk for injuries/accidents. Early information is important, as the risk is highest during the first 2 years following seizure onset.