



Highlights From the Annual Meeting of the American Epilepsy Society 2018

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Abstract

The American Epilepsy Society Meeting in New Orleans attracted more than 5900 attendees. There was a lively exchange of new science, innovation, education, clinical practice, and many other items related to epilepsy. Educational symposia were a major part of the meeting and explored varying topics of interest for all types of epilepsy professionals. This article reviews highlights of the meeting presented in major symposia. Topics ranged from how to treat varying aspects of epilepsy as a consultant in the hospital to finding the scientific underpinning of the interaction between sleep and epilepsy. Pros and cons of novel antiseizure medications, dietary, and stimulation treatments were discussed. Epilepsy may impair memory and we need to learn what is the pathophysiologic relationship. Febrile status epilepticus may have severe consequences for a later life with seizures. Epilepsy professionals should be very well aware of the ethical implications of devastating seizures and their associated disability. These are just a few select topics of the many that we need to study further to archive the final goal to improve the lives of patients with epilepsy.

Introduction

More than 5900 epilepsy professionals attended the Annual Meeting of the American Epilepsy Society in New Orleans November 30 to December 4, 2018. It was a vibrant get-together focused on epilepsy education, the latest breakthroughs in epilepsy science, collaborations with industry and advocacy partners and, most of all, professional exchange and discussion. The authors thank everybody who attended the meeting for their valuable contributions. The American Epilepsy Society would not be as dynamic without you. Especially, we would like to thank our volunteers in respective committees that worked diligently to organize excellent symposia and content. This is a brief summary of some the content of the major symposia in 2018, and we look forward to similar, excellent content for the meeting in Baltimore December 6 to 10, 2019. If you were not able to attend all sessions recordings are available at <https://www.pathlms.com/aes/>.

Fundamentals Symposium: Epilepsy on the Consult Service

Fred Lado, MD PhD, Aradia Fu, MD

The symposium addressed the intricate relationship between epilepsy and other medical conditions.

Dr Scott Mintzer kicked off the symposium with his talk “Epilepsy & Heart Disease: Tips for the Consultant.” He identified the impacts of anticonvulsants on the cardiovascular system and the interactions between antiepileptic drugs (AEDs) and cardiac medications. Hepatic enzyme inducing anticonvulsants are associated with worse lipid profiles and vascular risk markers and reduce the efficacy of some cardiovascular medications, such as statins.¹ Older anticonvulsants, such as carbamazepine, may even be associated with increased risk of myocardial ischemia. Dr Steven Pacia presented “Syncope and Other Seizure Mimics,” where he reviewed key clinical features that distinguish seizures from



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syncope and other seizure mimics such as migraine, transient ischemic attacks, metabolic disorders, nonepileptic psychogenic seizures, transient global amnesia, and sleep disorders. There is a broad differential diagnosis for episodic loss of awareness. Some, such as prolonged QT syndrome, should not be missed.² Dr. Andres Kanner led the discussion on “Do Psychotropic and Antibiotic Drugs Cause Seizures? A Review of the Evidence.” He reviewed selection of antibiotics and psychiatric medications that would minimize seizure risk. Therapeutic doses of serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants appear to be associated with reduced seizure incidence, though overdoses of these classes of medications can be associated with increased risk of seizures.³ Bupropion and clomipramine were the exceptions to the rule, and seizure risk was increased with these medications compared to placebo. Antibiotics may increase the risk of seizures. The mechanism by which antibiotic lower seizure threshold may be decreased GABAergic activity. Dr Page Pennell discussed the management of AEDs during pregnancy to optimize seizure control and pregnancy outcomes in her talk “Seizure Management during Pregnancy.” Her presentation reviewed the teratogenic risk of AEDs (particularly high with valproate as well as older AEDs) and other pregnancy outcomes including “small for gestational age” (greatest risk associated with topiramate, phenobarbital and zonisamide, and valproate).⁴ Valproate was also associated with lower IQ in childhood and increased risk of autism. On the other hand, folate prescribed before pregnancy or at start of pregnancy was associated with higher IQ and lower risks of autism. There are changes in pharmacokinetics of AEDs during pregnancy and dose adjustments are needed to maintain seizure control. Dr Jeanne Young discussed “Anticonvulsants and the Skin Hypersensitivity”. Dr Young emphasized the diversity in hypersensitivity associated with AEDs, distinguishing drug rash based on pathophysiology and clinical characteristics, and recognizing clinical features that could alert us to severe cutaneous adverse reactions. The most common type of reaction is a morbilliform rash with erythematous papules or plaques due to immune complex deposition and cell-mediated immunity. These rashes characteristically begin 7 to 10 days after starting medication and typically resolve in 2 to 3 weeks. Patients usually feel well, though they may complain of pruritis. Interestingly, in some cases it is possible to “treat through” the rash, or re-challenge later with the same medication, with the patient under close observation by dermatology. Signs characteristic of more severe drug reactions are swelling of the face, presence of pustules, bullae, or vesicles, dusky or painful lesions, mucous membrane involvement, or signs of systemic involvement. Morbilliform skin eruptions beginning later than expected along with systemic symptoms and patient feeling ill are more concerning for progressing to Drug Rash with Eosinophilia and Systemic Symptoms syndrome.⁵

Merritt-Putnam Symposium: The Neurobiology of Memory

Catherine A. Schevon, MD, PhD

The neurobiology of memory has long been a central issue in epilepsy, particularly for syndromes involving mesial temporal lobe structures. While Ramon y Cajal first detailed the neuroanatomical structure of the hippocampus more than 100 years ago,⁶ it was the well-known case of “H.M.” that revealed the prominent role of the hippocampal formation and related structures in declarative memory.⁷

Patients undergoing temporal lobe resection for control of pharmacoresistant seizures may experience postoperative memory decline. Preoperative reorganization of the posterior hippocampus with transfer of function to contralateral and extratemporal structures including anterior cingulum and insula may be a key factor in preservation of memory function,⁸ and there may be a role for memory functional magnetic resonance imaging studies in individualized outcome prediction.⁹ There is also evidence that the choice of surgical approach has important implications for postoperative memory outcomes.¹⁰

Even apart from surgical intervention, memory deficits are a common comorbidity in epilepsy. At the cellular level, seizure-induced epigenetic dysregulation likely plays an important—but little understood role. Abnormally regulated BDNF DNA methylation was explored in a rodent temporal lobe epilepsy model, and was shown to have a dual role in modulating both epileptiform abnormalities and memory impairments.^{11,12} Memory consolidation is an important mechanism supporting long-term memory that may also be disrupted by epileptiform activity. Studies of human multiscale and animal recordings demonstrated locally recorded cortical replay of waking patterns during subsequent sleep periods.¹³ This process involves an intricate coordination of cortical up and down states, hippocampal sharp-wave ripples and thalamocortical spindle activity, with distinct roles played by the anterior and posterior hippocampus. Finally, building on the previous year’s symposium, early results from a recent high-profile study of the use of cortical electrical stimulation to improve memory function were presented. In a promising development, successful enhancement of hippocampal-dependent memory in patients with epilepsy has now been reported with lateral temporal stimulation¹⁴ and independently in entorhinal white matter (but not gray matter) using θ -burst stimulation.¹⁵

Hot Topics Symposium: New and Emerging Treatments for Epilepsy and their Rational Approach

Michael R. Sperling, MD, Elinor Ben Menachem, MD, PhD

Emilio Perucca, MD, PhD, focused on the rational use of anticonvulsant medication and reviewed a systematic approach to sequencing and combining antiepileptic medications. Given



the extensive choice of treatments, an evidence-based systematic approach is important when treating patients.¹⁶ The literature contains a number of comparative studies, though more evidence is needed, particularly when planning polytherapy. Different clinical scenarios were provided to illustrate his approach, and he highlighted areas in which further knowledge must be obtained. This approach to therapy, which is driven by data and experience, offers a masterful way to treat epilepsy.

The second lecture, given by Dennis Dlugos, MD, “What’s in the Pipeline? Newly Approved and Almost Ready Antiepileptic Drugs” provided a review of both recently approved medications (stiripentol and cannabidiol) and drugs that are presently in the pipeline, but anticipated to enter the clinical arena. Professor Dlugos reviewed pivotal trial data, both with regard to efficacy and adverse effects. Pipeline drugs show promise for both generalized and focal epilepsy. It is hoped that the information provided in this lecture will enable the practicing physician to integrate the use of these agents into practice once they are available.

The third lecture, delivered by Barbara Dworetzky, MD, reviewed rescue therapy, with a particular focus on new and emerging treatments. Trials have been conducted employing several benzodiazepines, including diazepam, midazolam, and alprazolam. These new therapies may be administered intranasally, or in the case of alprazolam, by inhalation, though the latter agent has only recently entered the trial phase. Professor Dworetzky reviewed the pharmacology and trial results; these preparations do not require rectal administration and may prove a popular choice by patients and their families when rescue is needed.

The final lecture, given by Jukka Peltola, MD, reviewed deep brain stimulation of the anterior nucleus of the thalamus for intractable epilepsy. This therapy was recently approved by the Food and Drug Administration in the United States, but has been in use in Europe since 2011. Professor Peltola reviewed both clinical trial data and the European clinical experience, and proposed suitable indications for employing this therapy.

Pediatric State-of-the-Art Symposium: Metabolism-Based and Ketogenic Therapies for Epilepsy: A Translational Approach

Eric H. Kossoff, MD, and Jong M. Rho, MD

The symposium encompassed topics ranging from basic science, translational research, clinical trials, adverse effects, nutritional guidance, and possible anti-inflammatory benefits.

Dr Susan Masino covered “Cellular metabolism as a paradigm for experimental therapeutics in epilepsy.” She discussed the 4 major possible therapeutic targets of metabolism-based therapies: changes in blood and cerebrospinal fluid (elevated fats and reduced glucose), improved mitochondrial function and energy reserves, synaptic stability, and cellular changes including alterations in the gut microbiota.¹⁷ Dr Kristina Simeone then tackled “Metabolic approaches for treating complications and comorbidities of epilepsy.” She focused on how

these therapies (including diet but also involving triheptanoin, 2-deoxyglucose, decanoate, and ketone esters) have been shown in preliminary studies to benefit cognition, autism, behavior, sleep, and even SUDEP (Sudden Unexpected Death in Epilepsy).¹⁸ Dr Elizabeth Donner reviewed “Clinical evidence for metabolism-based therapies in children: trials and guidelines.” In her lecture, Dr Donner first covered the strong evidence from multiple randomized controlled trials for ketogenic diet therapy, then provided an overview of the updated 2018 revised international consensus guideline.¹⁹

The fourth lecture was given by Dr Anita Devlin and was titled “Ketogenic Diet for Infants?” Two specific epileptic encephalopathies affecting infants (infantile spasms and Dravet syndrome) have evidence for treatment response to ketogenic diet.²⁰ Dr Devlin ended by discussing the ongoing “KIWE” trial in the United Kingdom which has been enrolling infants 1 to 24 months of age into a randomized trial of the ketogenic diet versus further antiseizure drugs. Robyn Blackford, RD, provided a dietitian’s perspective on handling the adverse effects from these dietary interventions in a lecture entitled “Safety and prevention of risks from metabolism-based therapies.” Finally, Dr Stephane Auvin ended the symposium with a basic and clinical science lecture on “Are there anti-inflammatory effects of metabolic therapies?”, with a focus on refractory status epilepticus and Febrile Infection-Related Epilepsy Syndrome (FIREs).²¹ In summary, this symposium achieved its goal of highlighting how the ketogenic diet and other metabolism-based treatments have become “state of the art.”

Interprofessional Symposium: Ethical Considerations That Impact Professionals Caring for the Patient With Epilepsy

Janelle L Wagner, PhD, Madonna Plueger, APRN

This symposium addressed bioethics in 4 areas: (1) transition to adult care (2) delivery of behavioral health services using technology (3) self-management interventions and outcome measures, and (4) anti-seizure medication. General ethical principles, including respect for autonomy, nonmaleficence, beneficence, and justice as they pertain to comprehensive care of persons with epilepsy (PWE) were covered.

Dr Eric Racine articulated the nuances of respect for autonomy in the transition from pediatric to adult care for persons with neurodevelopmental disabilities. Autonomy includes 6 component abilities: (1) voluntariness (action of decision emerges from individual), (2) information (legitimate information available to take action), (3) control (able to take actions toward goals), (4) deliberation (motivation and reason for a choice), (5) authenticity (actions reflect the self, character, and coherence), and (6) enactment (decision actualized).²²

Dr Hamada Altalib discussed ethics in employing technology to deliver behavioral health care to PWE, including specifically challenges related to consent, privacy, confidentiality, and the patient–provider relationship. Insight into how



telehealth and mobile health can improve justice and equity by removing barriers to care such as transportation and resource disparities. The VA Epilepsy Center of Excellence was presented as a model for mobile behavioral health care. Appropriately implemented technology can revolutionize the range and standard of care.

Dr Martha Sajatovic covered self-management support and collecting behavioral outcomes. Given the high rate of mental health comorbidities and barriers to in-person behavioral health care, the SMART intervention contains one in-person session with a nurse educator-peer educator dyad and then 7 group sessions in a web-based format. Following SMART, PWE who had experienced a negative health event reported decreased depressive symptoms and improved quality of life versus people on a wait list.²³ There are ethical considerations, such as group confidentiality and the role of patients as peer educators. Findings from 5 pooled managing epilepsy well network randomized controlled trials demonstrated a reduction in depressive symptoms following self-management interventions. Research relies on integrated research datasets.²⁴ However, there are multiple ethical issues to consider, including protected health information, data sharing agreements, firewalls, and authorship.

Dr Viet Nguyen addressed ethics in selection of AED therapy. Beneficence and nonmaleficence must be balanced when identifying epilepsy management goals and related costs, and the role of justice was also discussed. Patients express concerns with AED changes, and clinicians must manage adverse effects to promote improved quality of life. Patients have a right to choose their therapy and there must be the balance of autonomy of choice with adequate treatment.

Annual Course—Controversies in the Management of Difficult Epilepsies

Lara E. Jehi, MD

Caring for patients with epilepsy is both a science and an art. This statement has never been more accurate than today. Faced with an exponential growth in diagnostic technology and novel therapeutics, the variety of choices that we have to make have become much more complex. Yet, robust data on comparative effectiveness and for evidence-based decision making are lacking. This information deficit is at the root of the significant variation in our practices, and suboptimal patient care. Considering several current controversies in the management of difficult epilepsies, some challenges stand out.

First, the frequency and indications for some tests that are considered cornerstones of our epilepsy management remain highly variable and require balancing multiple factors, including the treatment goals of the patients, risks, alternatives, and cost. The indication for a video EEG study is a perfect example. This inpatient testing is warranted to confirm the diagnosis of epilepsy and rule out psychogenic nonepileptic seizures in patients who continue to have seizures despite 2 or more adequate and appropriate antiepileptic drug trials. Conversely,

holding off the initiation of seizure medications until a diagnosis of epilepsy can be positively confirmed with video EEG is clearly inappropriate in patients at high risk of seizure related injuries, nocturnal convulsions with increased risk of sudden death in epilepsy, existing medical comorbidities (eg, ischemic heart disease; severe pulmonary dysfunction), severe ictal or postictal behavioral disturbance, and in resource-limited communities. Similarly, it is important to check the blood levels of seizure medications when changes in metabolism are expected (eg, pregnancy, dialysis) or in the context of suspected toxicity, but a routine practice of blood-level monitoring is a waste of time and resources.²⁵

Second, better evidence is needed to guide the initiation, choice, and discontinuation of seizure medications. For example, while traditional seizure medications such as clobazam may be highly effective to treat pediatric drop attacks, newer but significantly more expensive treatments (eg, Everolimus) are now available. Without robust analyses comparing the effectiveness and the cost of the traditional versus novel medication options, the choice of the ideal treatment remains controversial.^{26,27} Another glaring controversy is the timing and safety of medication withdrawal after successful epilepsy surgery where patient goals of independence and freedom from cost and adverse effects of seizure medications must be weighed against the risks of recurrent breakthrough seizures and downstream effects of reinstated seizure precautions such as driving restrictions.²⁸

Lastly, the recent increase in the use of invasive electroencephalography (EEG) recordings brings with it its own challenges to define indications and ideal methods for intracranial evaluations. Subdural electrodes have the advantage of permitting extraoperative ictal recordings in addition to mapping of eloquent cortex. Stereo EEG evaluations offer the ideal intracranial method for electroclinical correlations of an epileptic network.²⁹ Intraoperative electrocorticography has been equally successful in guiding surgical resections based on definition of epileptiform repetitive discharges. Given the lack of any direct comparative effectiveness studies and similar published long-term outcomes, the choice of one invasive EEG method over the other is largely dependent on the expertise of a center's neurosurgical and epileptology faculty.

In summary, controversies and epilepsy management abound, reflecting a need for more robust data.

2018 Presidential Symposium

Consequences of Prolonged Febrile Seizures in Children

Shlomo Shinnar, MD PhD

The symposium addressed topics related to the consequences of febrile status epilepticus (FSE) in children and in developing animals. The goal was to address the consequences including hippocampal injury and development of hippocampal sclerosis and mesial temporal lobe epilepsy.



Dr Dale C Hesdorffer addressed the epidemiology of status epilepticus (SE) and where FSE fits in. In new ILAE definitions of SE while for treatment purposes, the revised definition is 5 minutes, for the study of consequences, the 30-minute definition remains appropriate. Time to treatment unfortunately remains much longer than we would like. Mortality of SE, while primarily a function of etiology, remains substantial. Febrile status epilepticus rarely stops on its own without administration of AEDs.

Dr Shlomo Shinnar, who moderated the symposium, then discussed data on the consequences of FSE with an emphasis on results of the FEBSTAT study (“Consequences of prolonged febrile seizures in childhood”).³⁰ Hippocampal injury as reflected in increased hippocampal T2 signal on magnetic resonance imaging occurs in about 12% of cases. When hippocampal injury is present, there is substantial shrinkage of the hippocampi within a year and development of anatomic hippocampal sclerosis, though epilepsy has likely not yet developed. Children with evidence of acute hippocampal injury had a different cytokine profile than those without such evidence and from those with a fever but no seizure.³¹ As a group, children with FSE had somewhat smaller hippocampi at baseline than a control group with simple febrile seizures.³² Subsequent hippocampal growth is impaired in children with febrile SE. Dr David Masur then presented data on cognitive outcomes of children with FSE.³³ Data from prior studies, most of which did not explicitly study memory, were reviewed. In FEBSTAT, overall intelligence was normal. In children with evidence of acute hippocampal injury, memory as measured by the Wide Range Assessment of Memory and Learning particularly verbal memory, was impaired 5 years later. This is even in the absence of epilepsy. In children with normal imaging memory appears to be intact. Dr Tallie Z Baram then presented the animal data that help explain findings in humans. In immature rats, hyperthermia produces seizures. Susceptibility is influenced by genetic background but can be reliably reproduced in immature rodents. Febrile status epilepticus produces epilepsy after a silent period with duration of FSE determining severity of resulting epilepsy.³⁴ Febrile status epilepticus also results in enduring memory deficits with impaired function of hippocampal place cells. Inflammation may play a key role. An improved understanding of the mechanisms involved can inform future trials to prevent development of epilepsy and memory deficits following febrile SE.

Scientific Symposium: Losing Sleep Over Seizures—Does Sleep Matter

Kevin E. Chapman, MD, and Alica Goldman, MD, PhD

There is a known and close interaction between sleep and epilepsy. Understanding this complex relationship has far-reaching implications. It is now evident that risk of interictal activity and seizures in different human epilepsy types and syndromes varies depending on sleep states, and rapid eye movement (REM) stage is universally the least permissive to

seizures.³⁵ However, little is known about the effects of state transitions on seizures, and experimental research suggests an increased risk of seizures in transitions from REM.³⁶ But what may be the molecular correlates of the circadian variation of epileptic excitability?

There has been an explosion in research elucidating the underlying molecular mechanisms of the circadian rhythm and how this influences multiscale functions in the brain from basic cellular functions to larger scale networks. Recent studies have identified the molecular controls of the circadian clock that is regulated by the CLOCK/Brain and Muscle ARNT-like 1 (BMAL1) system. It has been shown that core clock genes, clock circadian regulator, CLOCK and BMAL1 contribute to epileptic excitability.³⁷ Interestingly, mTOR regulates BMAL1 proteostasis and TSC mouse models show abnormal circadian rhythms that can be corrected following genetic lowering of BMAL1 levels.³⁸ On the contrary, BMAL1 functions as a translational factor that links circadian timing to the mTOR signaling pathway³⁹ and BMAL1 knockout mice have lowered seizure thresholds.⁴⁰ Decreased CLOCK protein levels were seen in resected brain tissue from patients with intractable epilepsy and that these changes can alter cortical circuits.⁴¹ Tying together BMAL1/CLOCK and mTOR pathways may provide additional insights into epileptogenesis and potential novel drug targets.

Sleep is an important process in memory creation through regulation of normal synaptic homeostasis. Animal studies have demonstrated abnormal synaptic potentiation induced by epileptiform activity and seizures. In patients with focal epilepsy, a high density EEG study uncovered a widespread increase in slow wave activity, a marker of increased synaptic strength or excitability, that correlated with the burden of epileptic activity and cognitive impairment.⁴² Seizures during sleep can not only impair learning but increase mortality risk in patients with epilepsy. Clinical studies have demonstrated that sudden unexpected death in epilepsy (SUDEP) is more common during sleep. The mechanisms for this increased risk is unclear, but rodent studies suggest that serotonin is important in arousal, in postictal recovery of respiratory function, and as a modulator of seizure severity.⁴³ Improved understanding of the role of the serotonergic system in sleep, seizure susceptibility, and in the overall circadian regulation will be important in our search for preventative treatments for SUDEP.

Epilepsy Therapies Symposium: Practical Clinical Pearls for Advanced Outpatient Epilepsy Management in 2019

Lawrence J. Hirsch, MD, and Timothy A. Simeone, MD

In the first presentation on “Polypharmacy: Predictable and unpredictable interactions,” Dr Dean Naritoku highlighted the complexities of predicting drug interactions from established data. Older anti-epileptic drugs (AEDs) tend to have more predictable changes, primarily induction or inhibition, whereas newer agents are less predictable because they may induce



some CYP isozymes and inhibit others.⁴⁴ Finally, the newest agents may be least predictable for clinicians simply because of their limited experience. Thus, vigilance for interactions is always needed.

In the second presentation on “Improving measurements of seizure control, including use of wearables,” Dr Tobias Loddenkemper presented data on the low reliability of patient reporting of seizure frequency, partly but not only due to patients’ lack of awareness of their seizures. Fortunately, multiple convenient wearable devices for detecting seizure activity (mostly convulsive) have become or are soon to become available; some of these are Food and Drug Administration (FDA)-cleared and show promising data for reliable detection of tonic-clonic seizures. More sophisticated multimodality devices and software will soon follow.⁴⁵

In the third presentation on “Cannabidiol and medical marijuana: Use, misuse, and patient self-medication,” Dr Tyler E. Gaston defined important terms used when discussing cannabis products with patients and families, reviewed the current evidence for the use of pharmaceutical grade cannabidiol for epilepsy, and discussed issues with unreliable consistency of labeling of artisanal cannabis products. The only high-quality evidence to date is the use of pharmaceutical-grade cannabidiol for Lennox-Gastaut and Dravet syndromes, leading to US FDA approval with these indications.^{46,47}

In the final presentation, “Towards self-management of acute seizures: Expanding out-of-hospital treatment options,” Dr James Cloyd first discussed current approved and off-label options for management of seizure emergencies.⁴⁸ Products under development include intra-pulmonary, buccal, and intranasal formulations, some of which may be available within the next 1 to 2 years. He concluded his remarks by noting that rapid advances in seizure prediction technology coupled with anti-seizure delivery systems that result in therapeutic brain concentration within minutes have the potential to prevent seizures, which could change the paradigm for managing epilepsy.

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