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EXPERT REVIEWS

An update on epilepsy

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Mike R Schoenberg[†1], Alfred T Frontera[1], Ali Bozorg[1], Pedro Hernandez-Frau[1], Fernando Vale[1] and Selim R Benbadis[1]

[1]*University of South Florida College of Medicine, FL, USA*
[†]*Author for correspondence: Department of Psychiatry and Neurosciences, University of South Florida College of Medicine, 3515 E. Fletcher Ave., Tampa, FL 33613, USA*
mschoenb@health.usf.edu

64th Annual Meeting of the American Epilepsy Society and the 3rd Biennial North American Regional Epilepsy Congress

San Antonio, TX, USA, 3–7 December 2010

The understanding of seizures and epilepsy as a disease has accelerated to reflect advances in the understanding of the interplay of seizures and epilepsy on neurophysiology, neuroplasticity, sleep, neuropsychology, behavior and social functioning of the individual, which interact with and can be affected by an individual's quality of life, educational development and occupational success. Updates in the treatment of status epilepticus, epilepsy in children and adults (particularly women), and psychogenic nonepileptic seizures/attacks have been announced. There is increasing emphasis on untangling the interactive forces of new antiepileptic medications from epilepsy/seizures on the neurophysiological, neuropsychologic and psychiatric/behavioral functioning of individuals with epilepsy. The role of GABA in the pathophysiology of seizures and status epilepticus has led to novel therapy proposals. Neurostimulation technologies and neurosurgical procedures have improved the clinical outcomes of patients with epilepsy, and have led to important advances in understanding the neuropathophysiology of epilepsy/seizures and brain plasticity. For example, neurostimulation allows long-term *in vivo* electroneurophysiological recordings of specific brain regions that has not been previously possible in humans. The 64th Annual Meeting of the American Epilepsy Society and the 3rd Biennial North American Regional Epilepsy Congress provided state-of-the-art updates to scientific and clinical practice issues in the treatment of epilepsy.

The study of epilepsy and seizures spans the very best in translational research, from animal models that attempt to understand the pathogenesis of seizures, or help to evaluate the effectiveness of treatments, to clinical research with individuals across their lifespan to better identify, treat and, if possible, prevent epilepsy. The recent Annual Meeting of the American Epilepsy Society (AES) and North American Regional Epilepsy Congress provided an ideal forum to highlight state-of-the-art findings among scientists, practitioners and policy makers.

The 64th Annual Meeting of the AES and the 3rd Biennial North American Regional Epilepsy Congress is the largest professional organization of the Internal League Against Epilepsy, and attracts scientists and clinicians from the USA and across the globe. The scientific program included 15 scientific symposia and lectures, a variety of special interest group meetings, investigator workshops, platform sessions, the 18th Annual National Epifellows Foundation Scientific Forum and three poster sessions allowing for nearly 1000 poster presentations. The AES meeting is arguably the preeminent conference for scientists and clinicians interested in epilepsy.

Antiepileptic medications update

A variety of new antiepileptic medications (AEDs) have been approved for use in epilepsy in the past decade, and advances in knowledge as to their proposed mechanisms of action and potential for side effects and/or new indications were presented at the AES meeting. This year leading developments focused on lacosamide (LCM), retigabine (now ezogabine) and clobazam. LCM is a recently approved AED for the adjunctive treatment of partial-onset seizures. LCM demonstrated no effect on cognition or mood, based on a small (n = 18) sample of adults [1], and no effect on bone density in dogs [2]. An interesting finding was that side effects and discontinuation appear to be higher when LCM is associated with sodium channel blocking AEDs (phenytoin [PHT], carbobenzoxy, oxcarbazepine, lamotrigine) [3].

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Off-label use of LCM included efficacy in children [4,5], some efficacy in status epilepticus (SE) [6–8], and some efficacy in the idiopathic generalized epilepsies [9,10].

Ezogabine (previously retigabine) is not yet available in the US market, but demonstrated good efficacy and tolerability that was comparable to other newer AEDs [11–13]. Ezogabine has a different mechanism of action (K channel opener) and inhibits smooth muscle contractility, which has raised concerns about its effect on bladder function. However, a study presented data that demonstrated that any effect on bladder function is mild [14]. Finally, clobazam demonstrated efficacy in Lennox–Gastaut syndrome [15].

Status epilepticus: treatment updates

A variety of issues involving SE were presented at this AES meeting. SE is a life-threatening, neurologic emergency with mortality rates in adults ranging from 11 to 34% [16]. Benzodiazepines (particularly lorazepam) are the first-line treatment for SE, followed by PHT or fosphenytoin as second-line therapy [17–19]. First-line treatments were successful in terminating SE in approximately 55–65% of cases, while the aggregate response rate to second-line agents for patients who did not respond to first-line treatment was 7% [17–19]. Such a disparity in efficacy between first- and second-line agents suggests that time to treatment is a key factor in treating SE. Indeed, delayed treatment is associated with higher rates of refractoriness and increased mortality in SE [20–25]. While benzodiazpepines are efficacious in the early stages of SE, they are significantly less effective when administered later in the course of SE [18,22]. During the presidential and antiepileptic therapy symposia of the 2010 AES meeting, speakers addressed the role of GABAergic transmission in epilepsy and explained how it may provide both an explanation for this clinical phenomena and a theoretical framework for more effective treatments of SE.

Benzodiazepines work by binding to allosteric binding sites on the $GABA_A$ receptor, which ultimately results in a higher affinity of GABA for this receptor. In the normal adult brain, this higher affinity binding of GABA to the $GABA_A$ receptor leads to hyperpolarization of the neuronal membrane and inhibition of neuronal firing.

The lecture entitled '$GABA_A$ receptor trafficking during status epilepticus' discussed how during SE, there is an activity-dependent trafficking of certain synaptic $GABA_A$ receptors from the cell surface into the cell. This trafficking results in a reduction of the benzodiazepine-sensitive $GABA_A$ receptors and a reduction in $GABA_A$-mediated neuronal inhibition, which partially explains the development of benzodiazepine pharmacoresistance during SE. This model provides a molecular basis to support the clinical observation that it is imperative to treat SE early, and also suggests possible future therapeutic interventions. In addition, neurosteroids and anesthetics, which act through a separate subclass of GABA receptors, may be effective adjuvant treatments for benzodiazepine-refractory SE.

Lectures titled 'GABA and dynamic chloride regulation in health and disease' and 'GABA-induced depolarization: a tale of opposing forces' reviewed the roles of cation chloride cotransporters (KCC2 and NKCC) in determining GABA-gated chloride currents. This *in vitro* work demonstrated that GABA is excitatory in immature neurons, and provided a potential molecular mechanism to explain the clinical observations that GABA-ergic drugs are not consistently effective in controlling seizures in newborns and young infants. It also suggests new therapeutic targets, and the speakers summarized work demonstrating how to enhance the efficacy of phenobarbital in a neonatal seizure model via concomitant use of bumetanide. Bumetanide blocks the neuronal chloride cotransporter, which is at least partially responsible for the reversal of the effect of GABA from inhibition to excitation.

In a lecture entitled 'Novel therapies for neonatal seizures' data was presented which indicated traumatic and hypoxic injuries as well as ictal activity can reverse the effect of GABA-ergic stimulation from inhibitory to excitatory. As such, bumetanide may have a therapeutic role for the treatment of seizures after traumatic-, hypoxic- and ictal-induced neuronal injury when used in combination with the traditional GABA-ergic AEDs.

In addition to the role of GABA in seizures and SE, the effectiviness of other AEDs in the treatment of SE was also presented. In particular, the use of LCM for the treatment of SE received attention. LCM appears to have properties favorable for treating refractory SE owing to its mechanism of action, favorable pharmokinetic and side-effect profile, and availability in an intravenous (iv.) formulation.

The treatment efficacy and safety of LCM in SE treatment was provided by several studies. A retrospective study of iv. LCM in 19 patients diagnosed with refractory SE [6] found that 84.2% (16 patients) exhibited improvement in their EEG after the first day of treatment. A second study reported on 27 patients with SE treated with iv. LCM, observing cessation of SE in 33% (9 out of 27) of patients within 4 h of treatment and 77.8% (21 out of 27) of patients within 24 h [7]. In another study of iv. LCM in 19 consecutive patients with intractable SE or seizure clustering, iv. LCM appeared to terminate convulsive SE in one of six patients, nonconvulsive SE in three of three patients and seizure clusters in eight of ten patients [8]. The etiology of SE was not a predictor for response to LCM; however, patients with no prior history of seizures had a significantly better response to LCM than those with previous seizures ($p < 0.001$) [7]. Unfortunately, treatment nonresponders often eventually succumbed [7]. Few side effects were observed across the studies [6–8]. While 63% of patients in one study had seizure recurrence during hospitalization [6], the authors of these studies suggest emerging data indicate iv. LCM may be a safe and efficacious treatment for SE and seizure clusters.

Neuropsychology of epilepsy

The neuropsychological (cognitive and behavioral) comorbidities of epilepsy have been recognized for centuries, but the extent to which neuropsychological comorbidities are important in the prognosis and care of patients with epilepsy has received more emphasis in the past two decades [26–30]. The neuropsychological aspects of epilepsy were emphasized in the 2010 meeting through symposia, special interest group meetings, as well as platform and poster sessions. A symposium provided a detailed review of

neuropsychology in epilepsy and its application to the diagnosis and treatment of both children and adults with epilepsy. In addition, the 'Pediatric state-of-the-art symposium: identifying and managing the comorbidities of pediatric epilepsy' also featured a presentation that gave an overview of the cognitive and behavioral aspects of epilepsy in children. The special interest group meeting for neuropsychology highlighted the changing role of neuropsychology in the treatment and management of patients with epilepsy over the past decade, and discussed future directions for the science and discipline. Throughout the conference, attendees were offered an analysis of neuropsychological variables in the prognosis and treatment of patients with epilepsy.

Neuropsychological functioning is an important variable in affecting outcome and quality of life, including academic and social functioning and vocational success [26–30]. The symposia highlighted research demonstrating that neuropsychological deficits are often present at seizure onset in children with a variety of epilepsy syndromes [28,30]. The meeting highlighted research changing the perception of the so-called 'benign epilepsies', with children diagnosed with absence seizures exhibiting some neuropsychological deficits [30,31]. Reports have found adults with epilepsy identified at recent seizure onset have neuropsychological deficits [26–29]. At first recognized seizure, Fastenau reported neuropsychological deficits are more likely in children whom, at the initial evaluation, were found to have one or more of the following findings: exhibition of epileptiform activity on EEG, structural abnormalities on MRI (and/or diagnosed with a symptomatic/cryptogenic epilepsy etiology) or taking AEDs [30]. Importantly, academic deficits were not observed in children with first-onset seizures, and several modifiable factors were found that can decrease the risk of neuropsychological and academic deficits over time [30,31]. Data suggest improved seizure control, good sleep and positive family/caregiver adjustment can alter neuropsychological and academic functioning prognosis. Age of seizure onset during childhood affects the presence and severity of neuropsychological deficits [31].

Predicting neuropsychological outcomes from neurological surgery remained a focus for the meeting, and the benefits versus risks of intracarotid amytal/brevital procedure (Wada's test) were reviewed [32–34]. Wada's test results were again demonstrated to reliably predict verbal memory outcome following temporal lobe resection for patients with medication-intractable epilepsy [32–34]. While predicting memory and language outcomes remains an interest in neuropsychology following surgery for intractable epilepsy, the range of neuropsychological domains assessed has expanded, with research demonstrating that deficits in executive functions are present and affect memory and decision-making [35–37]. The meeting highlighted that neuropsychological function, and its self perception, is an important is an important comorbidity in epilepsy and has implications for an individual's social functioning, educational development, vocational status/success and quality of life.

Psychogenic nonepileptic seizures/attacks

Interest in psychiatric and psychological comorbidities among patients with epilepsy was highlighted by the symposia 'Annual fundamentals of epilepsy: psychogenic nonepileptic seizures', which provided an overview of the diagnosis and treatment of psychogenic nonepileptic seizures (PNES)/psychogenic nonepileptic attacks (PNEA). The symposium was well organized and provided presentations to diagnose and treat PNES in adults and children. While PNES contributes to significant difficulties in psychosocial functioning and to medical comorbidity, effective treatment is available. Lafrance presented an overview of PNES treatment and the results of a randomized clinical trial evaluating the effectiveness of sertraline. To date, there are only 24 publications related to the treatment of PNES. Initial results of his randomized clinical trial demonstrated some promising results to reduce and, in some cases, eliminate PNES. Additional treatment information was provided at the AES meeting [38]. In a retrospective analysis, 83% of patients with PNES (n = 12) exhibited either resolution or significant improvement of PNES 6 months after initiating treatment. Predictors of improved outcome included prompt diagnosis, referral to psychiatric treatment and initiation of selective serotonin reuptake inhibitors, as well as management of generalized anxiety disorder. Presence of borderline personality disorder was a risk factor for poor treatment response. Another treatment modality explored for PNES has been eye movement desensitization and reprocessing (EMDR), and Kelly and Bozorg reported that 14 of 23 patients with PNES completing EMDR treatment protocol had complete resolution of PNES [39]. The semiology of PNES in children was found to differ from adults, based on a retrospective review of 44 children diagnosed with PNES [40]. In children, 'ictal' eye closure and pelvic thrusting are not reliable indicators of PNES [40], but have been behaviors associated with PNES in adults [41,42]. Stuttering and weeping were not observed in children, but are frequently seen in adults with PNES [41,42]. Unlike adults, inadequate family support was observed more than abuse, which is opposite of that observed in adults [40]. PNES is not a unitary syndrome, and subtypes of PNES based on whether the PNES exhibits excessive motor activity (hypermotor) or a lack of motor activity (hypomotor) have been proposed and appear to affect the success rate in inducing PNES based on the behavioral presentation (so-called 'ictal' features) [41–43]. Izadyar *et al.* found 92% of patients with hypermotor-type PNES were successfully induced, while only 65% of patients with hypomotor-type PNES were induced [43]. Despite the advances in PNES treatment above, another study highlighted that PNES remains a syndrome that is difficult to diagnose and treat [43]. Hussain *et al.* found that among a sample of first responders, 35% of emergency medical technicians (EMTs) and 20% of emergency room physicians had never heard of the term PNES [44]. Moreover, of those familiar with the PNES term, 55% of EMTs and 70% of emergency room physicians had no formal training in the diagnosis or treatment of PNES [44]. These data argue that neurologists with expertise in PNES should work with EMTs and emergency room physicians to raise diagnostic and treatment awareness of PNES [44].

Neuroimaging in epilepsy updates

Neuroimaging is a critical part of the evaluation for epilepsy surgery. Indeed, neuroimaging has led to proposed changes in the classification of epilepsies, with fewer epilepsies being labeled as cryptogenic/probably symptomatic as the number of epilepsy

syndromes with definitive structural abnormalities are identified [45]. Data have established that 3 Tesla (3T) MRI provides superior image quality, detection of structural lesions and characterization of lesions [46–48]. The application of MRI diffusion-tensor imaging (DTI) and magnetic resonance spectroscopy, along with magnetoencephalography (MEG), are at the forefront in enhancing the ability to identify brain abnormalities to aide in the diagnosis and treatment of epilepsy [46,47]. Using 3T MRI and DTI imaging, researchers can assess the integrity and orientation of white matter pathways, which can detect abnormalities in mesial temporal structures not previously identified with more traditional MRI sequences in patients with temporal lobe epilepsy [46]. Further application of 3T DTI can identify microscopic abnormalities in white matter that may be associated with epileptogenesis and seizure propagation [48]. The importance of MEG and magnetic source imaging (MSI) were highlighted in several presentations, and the advantages in spatial and temporal acquisition of MEG/MSI provides a noninvasive method to identify receptive and expressive language areas in patients who are candidates for surgical treatment (for example, see [47]). The new functional neuroimaging technologies may have advantages over the more invasive Wada's test to localize and lateralize language (and potentially memory) functions (for example, see [47]).

Unfortunately, patient safety issues can limit the application of new imaging technologies, and patients undergoing vagal nerve stimulation (VNS) therapy is a group where safety concerns have prevented patients from benefiting from advances in neuroimaging, including 3T MRI imaging. However, data presented at the 2010 AES meeting demonstrated safety in patients with VNS when selected 3T MRI sequences were obtained [49]. These data offer hope that the advances in neuroimaging will be available in the near future to patients in which safety concerns have previously prevented their application.

Epilepsy surgery

The 2010 AES meeting brought together an extraordinary spectrum of expertise in neurological surgery for the treatment of patients with epilepsy. Sperling *et al.* demonstrated that patients who are seizure-free after epilepsy surgery have low mortality rates indistinguishable from the general population [50], consistent with the hypothesis that surgery reduces excess mortality from epilepsy. Neurosurgery treatment for medication-refractory epilepsy in infants and children remains an area of active research, and PET and SPECT imaging provides useful information in planning surgery for children [51,52]. Consistent with previous data, psychosocial outcome is improved among patients whom were seizure free [53,54].

Surgical intervention is an established treatment for medically refractory partial (focal) epilepsies. However, surgical treatment is challenged by a consistent failure rate of 10–40% among selected patients. Data presented at the meeting offered additional evidence that repeat surgery can be of benefit to patients whom continue to have seizures after a first surgical treatment. Risk factors for poor outcome from surgical treatment included extratemporal resection, dual pathology and no lesion identified on MRI structural neuroimaging. Seizure freedom was observed in cases where extension of the previous resection site was carried out and a lesionectomy was completed. Minimal complication or expected neurologic deficits were seen with repeat operations. Data established that re-evaluation and reoperation can be effective to obtain seizure freedom for patients with intractable seizures [55–57]. Early discontinuation of AEDs was not found to lead to seizure recurrence among patients who had undergone surgical treatment for refractory epilepsy. Most likely, early AED discontinuation unmasks surgical failure but not at the expense of eventual seizure freedom [58,59]. Data continue to establish the importance of surgery in the treatment of medication-intractable epilepsy.

Neurostimulation update

Neurostimulation is an increasingly appreciated treatment modality for patients with epilepsy, and was a hot topic at the 2010 AES meeting. Four modes of stimulation were discussed: the responsive neurostimulation (RNS™) system, deep brain stimulation (DBS) of the anterior nucleus of thalamus, external trigeminal nerve stimulation (ETNS) and VNS. New data regarding the first three are highlighted below, while VNS therapy for medically refractory epilepsy continues to demonstrate efficacy in limited patient samples worldwide.

Responsive neurostimulation is a cranially implantable investigational device connected to depth or subdural electrodes for patients with refractory partial (focal) epilepsy. The device also includes a programmer and a web-based interactive database. Long-term follow-up data for the RNS system in adults with refractory partial (focal) epilepsy were presented in a platform session [60]. At 2 years after RNS implantation, the median percentage seizure reduction was >40%, and the 50% responder rate was >45%. After 3 years, the 50% responder rate increased to 53%, suggesting efficacy was maintained, as well as a possible reduction in seizure frequency. Adverse event rates remained stable over time. Suicide rates in patients with RNS were similar to historic controls [60]. The location of seizure onset did not affect efficacy in a small sample of patients. In addition to treatment of intractable epilepsy, the RNS system allows for electrocorticography and recording of seizures from the implanted electrodes. Monitoring localization of seizure onset in 15 patients with known multifocal epilepsy found that seizures remained lateralized to one hippocampus for an average of 16 days (range was 4–39 days) after implantation of the RNS system before a seizure was recorded in the contralateral temporal lobe [61]. While preliminary, these data may have implications for patients undergoing invasive EEG evaluations – such that these data may be falsely lateralizing when using temporary implanted electrodes.

A promising new therapy for intractable epilepsy is ETNS [62]. Previously, initial efficacy for ETNS was reported for 13 patients who underwent bilateral supraorbital ETNS and were observed to have an average seizure reduction of 59% after 12 months of stimulation [62]. Data presented at the 2010 AES meeting extended the potential of ETNS for the treatment of refractory epilepsy with data for safety/tolerability, as well as proposing a potential mechanism of action [63,64]. Acute (1-h) and long-term (6-month) safety and tolerability of ETNS were good, without significant changes in heart rate or blood pressure [64]. Skin irritation was the most common

side effect, which improved with reducing the duration of stimulation or using hydrocortisone 1% cream. The exact mechanism of ETNS is not known, but could be, in part, due to the suppression of neuronal firing using intrinsic cortical inhibitory mechanisms [63].

The application of DBS in the treatment of epilepsy is an important potential treatment modality, and outcomes of bilateral anterior thalamic nucleus DBS were presented for two patient groups with intractable epilepsy [65,66]. While these studies were open-label (subjects knew the treatment condition), patients with intractable partial (focal) epilepsy who had failed surgery and had no identified lesion on MRI (n = 6), and two patients with Dravet syndrome, had a dramatic reduction in seizure frequency following bilateral anterior thalamic nucleus DBS [65]. This research contributes to the growing excitement for DBS as a treatment option for patients with intractable epilepsy. Patients with partial (focal) epilepsy may be offered DBS in Europe, while nonexperimental treatment with DBS in the USA is awaiting more data.

In summary, the 2010 AES annual meeting provided a forum for a broad spectrum of experts in the diagnosis and treatment of epilepsy and seizures to present cutting edge science and clinical practice, and promote social awareness for this debilitating disease. This meeting report highlights the advances in the diagnosis and treatment of epilepsy and seizures.

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Mike R Schoenberg is a member of the Healthcare Reform Workgroup and the Practice Management Committee of the American Epilepsy Society. Ali Bozorg serves on the speakers bureau for UCB Pharma. Selim R Benbadis serves as a consultant or a speaker for Cyberonics, GSK, Lundbeck, Sleepmed–DigiTrace, UCB Pharma and XLTEK. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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