

# Annual Course / From Then to Now: The Evolving Spectrum of Epilepsy Care

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## Abstract

Understanding the evolution of clinical tools and models of care is fundamental to advancing the field of epilepsy. The 2025 American Epilepsy Society Annual Course examined the expanding spectrum of epilepsy care through the integration of multi-specialty collaboration, innovative diagnostic modalities, and surgical and nonsurgical therapeutic interventions. The course underscored significant global advancements in epilepsy research and practice. This comprehensive review synthesizes key educational insights from the program, offering a critical perspective on the ongoing transformation of epilepsy care.

## Keywords

annual course, evolution, epilepsy, seizure, AES, global, advancements, therapeutics, diagnostics, multispecialty care

## Introduction

Evolution is a natural process of change and development leading to growth, innovation, and transformation. In medicine, evolution is also intentional, opening doors to discovery, progress, and advances in diagnosis and treatment. In this comprehensive review, we will delve into the evolution of epilepsy care over time with special emphasis on the development of multi-specialty care, diagnostic tools, medications, and surgical treatments. We will then explore the impact of these changes on a global scale.

### *Better Together: Multispecialty Care*

Epilepsy is more than just seizures. “Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.”<sup>1</sup> Treating all symptoms and comorbidities our patients experience as part of this complex condition often requires the coordinated participation and expertise of multidisciplinary teams. Multispecialty care in epilepsy offers this unique collaboration, particularly in the areas of neuropsychiatry, stroke and dementia, and neurocritical care, where it results in cost effective, higher quality care, and patient satisfaction.

**Neuropsychiatry of Epilepsy.** For centuries, the neuropsychiatry of epilepsy was mischaracterized as supernatural. Advances in neurophysiology and neuroimaging recontextualized epilepsy as a brain-based disorder, though its complex interplay with mood, cognition, and behavior continues to challenge clinical boundaries between neurology and psychiatry. The bidirectional relationship between epilepsy and psychiatric conditions suggest shared underlying pathophysiology. However, stigma and misinformation have led to inadequate psychiatric treatment in people with epilepsy, thus worsening overall prognosis.

Current literature strongly supports an interdisciplinary approach to the neuropsychiatric care of people with epilepsy, as both seizure control and comorbid psychiatric conditions impact quality of life. Psychopharmacological strategies are increasingly reviewed to minimize seizure risk, while managing psychiatric symptoms, reflecting a shift toward personalized, interdisciplinary approaches in epilepsy care. Additionally, neuromodulatory techniques, such as vagus nerve stimulation

and responsive neurostimulation (RNS), have demonstrated efficacy in improving seizures and mood.<sup>2,3</sup>

**Stroke, Dementia, and Epilepsy.** Poststroke dementia (PSD) includes all types of dementias occurring after stroke, irrespective of their cause. This concept is useful for reducing the risk of dementia after stroke, which is associated with poor functional outcome and increased mortality. Dementia after stroke triples within the first year of stroke. Stroke patients also have a 20-fold increased risk of seizures compared with those without stroke. Stroke patients with seizures have nearly 3 times increased risk of dementia, which could be explained by the presence of epileptiform activity in about 40% of patients with Alzheimer’s disease, the most frequent pathology of PSD, and the observation that epileptiform activity accelerates cognitive impairment. Despite the evidence, specific issues of secondary prevention in patients with PSD are not addressed in any guidelines. There have also been no trials specifically done to evaluate the benefit of targeting seizures for PSD prevention.<sup>4,5</sup>

**Neurocritical Care—Controversies in Post Anoxic Seizures.** Comatose patients after cardiac arrest (CA) routinely undergo multimodal prognostication in ICUs, including clinical, neurophysiological, radiological, and biological markers. Continuous EEG (cEEG) is often recommended: it allows detecting more information, albeit at higher cost. Nevertheless, observational data and an ancillary analysis of a randomized trial<sup>6</sup> do not show any impact on prognosis compared to repeated routine EEG (rEEG).

In line with early observations, the TELSTAR trial showed that treating patients with rhythmic or periodic EEG patterns, often accompanied by myoclonus, does not improve prognosis.<sup>7</sup> However, the subgroup with early Lance–Adams syndrome (with concomitant preserved EEG background, delayed status epilepticus (SE) appearance, favorable multimodal prognostication,<sup>8</sup> who may benefit from antiseizure medication (ASM) and sedation, was probably under sampled. Waiting for better trials, it seems reasonable to concentrate therapeutic resources on these relatively few patients. Contrary to the assumption that phenytoin represents a mainstay treatment for SE, convergent observations in patients after CA suggest favoring antimyoclonic compounds.



## Tools at Work: Diagnostic Progression

This review highlights particularly promising changes in the field of genetics, imaging, and wearable devices. In a world at the verge of artificial intelligence (AI) revolution, it certainly seems like the advent of high-power computing capabilities will refine tools in these promising areas to power the diagnostic tools of the near future. Our authors provide a glimpse of the diagnostic changes that have a notable impact on our patients' care.

### *Evolution and Advancement of Neuropsychological Testing.*

Neuropsychologists have long played an important role in the care of patients with epilepsy, particularly in presurgical evaluations. These specialists conduct comprehensive assessments that provide objective measurements of cognitive and emotional/behavioral functioning. The role of the neuropsychologist on the epilepsy team has evolved significantly over time. Outpatient evaluations continue to provide information about baseline cognition, localize and lateralize brain dysfunction, anticipate cognitive risks of surgery, and identify comorbidities such as mood disorders that may affect outcomes. The development of a cognitive diagnostic classification system in 2021 facilitated identification of specific cognitive phenotypes across epilepsy syndromes, allowing a more nuanced understanding of brain-behavior relationships, postsurgical cognitive outcomes, and the neurodevelopmental and potential neurodegenerative trajectories of epilepsy.<sup>9</sup> Neuropsychologists also increasingly develop and administer tests for mapping cognitive functions during treatments within inpatient monitoring units or intraoperative settings.<sup>10</sup>

**Updates in Epilepsy Genetic Testing.** Genetic factors have long been suspected to influence most epilepsies and genetic testing is now increasingly recognized as crucial in epilepsy diagnosis and management. The development of chromosomal microarrays, large gene panels, and exome and genome sequencing over the past two decades transformed our understanding of the genetic mechanisms of epileptogenesis. Individuals with early onset epilepsy, neurodevelopmental disorders, or structural brain malformations are the most likely to receive a genetic diagnosis<sup>11</sup>; but broader testing is expanding our understanding of the clinical spectrum of genetic epilepsies. Similarly polygenic risk assessment and somatic gene variation analysis are adding to our understanding of epilepsy. A diagnosis impacts medical decision making, prognosis and family planning.<sup>12</sup> However, there are still significant gaps in our understanding of epilepsy genetics and gaps in access to testing. As we move toward personalized healthcare and gene therapy, we will need to close these gaps.

**Presurgical Planning: Single-Photon Emission Computerized Tomography and Magnetoencephalography (MEG).** Ictal single-photon emission computerized tomography (SPECT) (and interictal MEG) has traditionally been used for localizing seizure foci, but recent work emphasizes its superior value for mapping broader patient-specific epileptic networks. By

dynamically adjusting SISCOM thresholds, relevant hyper- and hypoperfused regions can be identified. Multimodal approaches (including resting state MEG & stimulation-related stereo-EEG [SEEG]) reveal that hyperperfused regions are not random and correspond to nodes with strong connectivity to the epileptogenic focus, while hypoperfused regions form a distinct but also interconnected network.<sup>13</sup> Ictal SEEG further validates the concept of neurovascular coupling with hyperperfused regions exhibiting a boost in high-frequency activities and suppression of slow rhythms.<sup>14</sup> Importantly, ictal SPECT should not be seen as a mere localization tool, but rather as a noninvasive method to delineate individualized seizure networks. Integrating SISCOM patterns with SEEG planning improves sampling of seizure-activated nodes, while broader network analysis may guide therapies beyond resection, including nodal ablation, localized drug delivery, or targeted neuromodulation.

Magnetoencephalography has direct clinical applications which can help us better manage individuals with drug-resistant epilepsy (DRE). Magnetoencephalography does not lose signal due to volume conduction, is more precise in temporal and spatial domain (3–4 cm<sup>2</sup> and picks up tangential dipoles in areas difficult to reach by EEG). It provides clinically relevant, nonredundant information which can alter the approach to surgery in one-third of the patients and may prevent invasive intracranial monitoring procedures in 19%. It assists in narrowing down the area to be implanted by SEEG and in surgical failures. Comparing the diagnostic performance of MEG to SPECT-SISCOM revealed MEG as a useful alternative for patients who cannot undergo SPECT. It has also been shown that MEG discharges influenced surgical decision making in as many as 63% of the patients.<sup>15,16</sup>

### *New Era of Seizure Monitoring—Wearables and Implantables.*

Wearable devices have the potential to improve patient safety through real-time seizure detection, reducing morbidity and mortality associated with convulsive seizures, and enhancing patient care by accurately quantifying seizure burden.<sup>17</sup> Several noninvasive wearable devices have achieved high sensitivity (up to 100%) and low false alarm rates (as low as zero during sleep) in phase 3 validation studies.<sup>17</sup> The International League Against Epilepsy recommends their use in patients with bilateral convulsive seizures who sleep alone but can receive rapid help after detection.<sup>17</sup> Promising results have also been demonstrated for objective seizure quantification using subcutaneously implanted EEG electrodes with automated detection supervised by expert review,<sup>18</sup> as well as heart-rate-variability-based detection linked to automated behavioral testing.<sup>19</sup> Using AI, seizure forecasting with subcutaneous EEG has shown encouraging results.<sup>20</sup> However, large prospective studies are needed to establish the clinical value of these devices.

## Progress with Therapy: Drugs and Surgery

Propelled by a more in-depth understanding of complex epilepsy networks and disease states, therapeutic inventions,



whether with medications, surgical, or noninvasive methods, have made enormous advances over time. Join me to dive into this evolutionary realm in areas of new onset refractory SE (NORSE), etiology-based epilepsy surgery, noninvasive neuromodulation methods, and thalamic stimulation surgery.

**New Onset Refractory SE Treatment: ASMs First or Immunotherapy First?** New onset refractory SE is a rare and devastating condition characterized by de novo onset of refractory SE (RSE) without an identifiable acute or active structural, toxic, or metabolic cause. When fever is part of this clinical presentation, the term FIRES (Febrile Infection-Related Epileptic Syndrome, a subcategory of NORSE) is applied. Any age group can be affected<sup>21</sup>; the mortality rate is high, and survivors often suffer from refractory seizures and adverse neurocognitive sequelae. The cause is unknown in greater than 70% of cases despite intensive investigations.<sup>22</sup> Treatment guidelines recommend standard RSE management with ASMs first and initiation of additional treatments, primarily immunotherapy, advised within 72 h of diagnosis.<sup>23</sup> The evidence for a primary role of the immune system in the onset, etiology, response to treatment and long-term outcomes is growing. Most research has centered around cytokines, pro and anti-inflammatory signaling molecules, associated with the innate immune system. Immune treatments used in NORSE have been targeted to specific cytokines (e.g., IL-1 anakinra and IL-6 tocilizumab) but not all patients show response to these treatments, questioning their causative role. Current debates are whether immunotherapy treatment is early enough, and which immunotherapy is most effective. A recent observational study found that cytokines can distinguish specific “biological” clusters of cryptogenic NORSE patients, which suggests that variations in the underlying immune mechanisms contribute to differential treatment responses.<sup>23</sup> These findings underscore the importance of personalized therapeutic strategies, potentially targeting specific inflammatory pathways, to optimize clinical outcomes in this challenging condition. The first randomized controlled trial (COMBAT-NORSE) will soon be underway to compare anakinra and tocilizumab, two promising second-line immunotherapies, and will hopefully shed light on how to better improve outcomes for individuals affected by NORSE.

**Etiology-Based Epilepsy Surgery.** Etiology-based epilepsy surgery represents a modern, personalized approach where interventions are adapted to the underlying factors and network dynamics of each patient’s seizures. Advances in imaging and electrophysiology allow tailored approaches, including diagnostic, resective, ablative, and neuromodulatory surgeries. SEEG provides high-resolution mapping of seizure networks, even in MRI-negative or multilobar cases, safely guiding individualized surgical plans, even in young pediatric patients. Laser interstitial thermal therapy, a minimally invasive ablative technique for focal or lesional epilepsy, achieves seizure freedom rates almost as high as resective surgeries, with reduced surgical morbidity.<sup>24</sup> Responsive neurostimulation delivers targeted, responsive brain stimulation, with 60%–

70% of patients achieving  $\geq 50\%$  seizure reduction, including those with multifocal or generalized epilepsy.<sup>25</sup> Together, these individualized protocols, and early referrals, facilitate tailored, successful, mechanism-based interventions, improving outcomes for patients with heterogeneous epilepsy etiologies.

**Beyond Conventional Therapies—Hope or Hype?** Noninvasive neuromodulation is an evolving area for treatment of DRE who are not candidates for resective or ablative surgery. Treatment modalities include devices that deliver electrical or magnetic stimulation, such as transcranial magnetic stimulation and transcranial electrical cortical stimulation, which includes direct current and alternating current stimulation; and devices that deliver nonablative focused ultrasound. Differences in stimulation parameters, timing of the therapy, that is, acute treatment of focal SE or outpatient treatment of refractory focal epilepsy, and target localization complicate direct comparison of the techniques. While case reports and small case series report promising results, these await confirmation in randomized clinical trials.<sup>26,27</sup>

**Thalamic Stimulation for Epilepsy.** The thalamus plays a pivotal role in epileptic network dynamics, serving as both a relay and a driver of seizure propagation. Over the past decade, RNS has evolved to target thalamic network hubs for both seizure detection and stimulation. Thalamo-cortical RNS was first applied in regional onset epilepsies and later extended to bilateral centromedian (CM) stimulation for idiopathic generalized epilepsy (IGE).<sup>28</sup> Ongoing clinical trials are evaluating CM-RNS for IGE and bilateral thalamo-cortical RNS for Lennox–Gastaut syndrome. Concurrently, SEEG methods have advanced to define the early engagement of thalamic nuclei in regional and rapidly generalizing seizures with diffuse or multifocal onset, guiding target selection for neuromodulation.<sup>29</sup> This approach is further supported by registry data showing reduced efficacy of anterior thalamic deep brain stimulation when seizure circuits extend beyond temporal–frontal networks. Unlike duty-cycle stimulation devices, RNS records and responds to individual epileptiform events, facilitating medication titration and minimizing stimulation during normal physiological activity.

### Think Big: Global

Epilepsy has no borders; but it is experienced differently across the globe by various communities based on local accessible resources, including in our own vicinities. It is an unpleasant reality that on a local, national, and international level patients experience inequities in care. This section emphasizes key areas of epilepsy evolution on a global scale. It challenges the use of resources and how things can be done differently and yet effectively in different areas, throughout the world, and with universal collaboration to advance care for all people living with epilepsy across neighborhoods and across continents.

**Bridging Financial Gaps.** Epilepsy care worldwide is persistently undermined by disparities between needs and available resources—financial gaps—which reflect structural neglect in budget priorities, workforce investment, diagnostic access, and policy frameworks and are evident across both high-income and low- and middle-income countries. Addressing them requires tailoring solutions to local cultural, social, and economic contexts, while amplifying the often-unheard voices of those most affected. Strategies include scaling cost-effective technologies such as tele-epilepsy and low-cost diagnostics, improving access to generic and even branded ASMs, integrating epilepsy into primary health systems, and aligning investor incentives for stakeholders across government, philanthropy, and private sectors. Incremental and disruptive innovations are needed to close gaps, supported by transparent accountability and partnerships that reframe costs as long-term investments. Ultimately, bridging these financial gaps, increasingly magnified by the impacts of climate change, depends on equity-driven policies and trust-based global and local collaborations that will finally enable sustainable change.<sup>30,31</sup>

**Bigger Bang for Your Buck: REEG or cEEG?** Continuous EEG monitoring is the cornerstone of detection of seizures and SE in critically ill patients. Over the past decades, it has experienced wide acceptance and expanded popularity for additional indications, such as grading encephalopathy, assessing sedation level in increased intracranial pressure and monitoring for delayed cerebral ischemia in subarachnoid hemorrhage, and assisting prognostication in CA and traumatic brain injury.<sup>32</sup> Additionally, large studies have suggested that cEEG improves patient outcomes and survival, with the caveat that it may prolong hospitalization.<sup>33,34</sup>

Despite these advances, implementing cEEG monitoring requires advanced technological infrastructure and expertise for application and interpretation, which are not globally available. The data on cEEG cost-efficiency compared to rEEG in public health systems where it is not adequately reimbursed, and on patient outcomes that are largely dependent on underlying etiology and comorbidities are under question. In addition to stewardship of resources, prolonged recordings must be also leveraged against the cost and morbidity associated with transferring patients to specialized facilities, as well as the risks of skin breakdown and reduced patient mobilization.<sup>35</sup>

Thus, the trade-off between cEEG and rEEG needs to be evaluated in the context of the individual patient and the health system where care is delivered. The choice should rely on the pretest probability of a history of preceding seizures in conjunction with the clinical examination, neuroimaging and laboratory findings, as well as the posttest probability provided by the initial EEG recording. For that matter, validated tools have been created (e.g., 2HELPS2B score) to give guidance to treating physicians.<sup>36</sup>

Point-of-care EEG systems in conjunction with quantitative tools and AI will hopefully simplify the selection process in the future. Ultimately, the choice between cEEG and rEEG will

remain patient-tailored and physician-driven and will largely depend on bridging the gap between resource-rich and resource-limited settings.<sup>37</sup>

**Reproductive Health and Epilepsy.** Reproductive health has significantly evolved over the years, aligned with increasing human and reproductive health rights of women. Key developments include observations of similar fertility for women with epilepsy (WWE) compared to women without epilepsy (WWOE) and when needed, fertility therapy success rates for WWE similar to WWOE.<sup>38,39</sup> Preconception counseling is a crucial, underutilized window for (1) pregnancy counseling, (2) ASM optimization, and (3) initiation of folic acid supplementation, though the optimal dose is unclear.<sup>40</sup> Worldwide, independent registries consistently observe dose-dependent risk of major congenital malformations with in utero exposure to many ASMs, especially valproate, topiramate, and phenobarbital.<sup>41</sup> Equally concerning, poorer behavioral and neurodevelopmental outcomes in children with valproate exposure are observed as far out as 6 years of age.<sup>42</sup> Therapeutic drug monitoring is increasingly used to inform dose adjustments in pregnancy of ASMs especially ASMs with observed lowered serum levels in pregnancy (i.e., lamotrigine, levetiracetam, oxcarbazepine). Such dose adjustments have been associated with seizure stability during pregnancy.<sup>43,44</sup>

## Conclusion

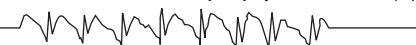
Evolution is the essence of progress in science, in thought, and in the pursuit of human well-being. The evolution of ideas, clinical tools, and models of care continues to shape the landscape of epilepsy treatment, driven by the enduring imperative to improve the lives of the 1%–2% of people worldwide living with this condition. Epilepsy itself embodies complexity and diversity: a heterogeneous disorder arising from multiple etiologies, with variable presentations, intricate symptomatology, and far-reaching neuropsychiatric comorbidities.

The evolution of epilepsy care reflects this complexity, advancing through a broad spectrum of interventions from pharmacological and surgical to neuromodulatory, dietary, and psychotherapeutic approaches, each refined by deeper understanding of the condition, multispecialty collaboration, and genetic underpinnings. As our conceptual and technological frameworks evolve, so too does our capacity to envision and execute more precise and effective care.

Ultimately, the evolution of epilepsy care is not a linear one; the solutions of yesterday may be reconsidered tomorrow or discarded altogether. The real meaningful trajectory is more a moral one anchored in the unwavering commitment to enhance the quality of life for every individual affected by epilepsy; that is, the path worth pursuing, from then to now and for generations to come.

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