Epilepsy priorities in Europe: A report of the ILAE-IBE Epilepsy Advocacy Europe Task Force

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Epilepsia, 56(11):1687–1695, 2015
doi: 10.1111/epi.13201

Summary: The European Forum on Epilepsy Research (ERF2013), which took place in Dublin, Ireland, on May 26–29, 2013, was designed to appraise epilepsy research priorities in Europe through consultation with clinical and basic scientists as well as representatives of lay organizations and health care providers. The ultimate goal was to provide a platform to improve the lives of persons with epilepsy by influencing the political agenda of the EU. The Forum highlighted the epidemiologic, medical, and social importance of epilepsy in Europe, and addressed three separate but closely related concepts. First, possibilities were explored as to how the stigma and social burden associated with epilepsy could be reduced through targeted initiatives at EU national and regional levels. Second, ways to ensure optimal standards of care throughout Europe were specifically discussed. Finally, a need for further funding in epilepsy research within the European Horizon 2020 funding programme was communicated to politicians and policymakers participating to the forum. Research topics discussed specifically included (1) epilepsy in the developing brain; (2) novel targets for innovative diagnostics and treatment of epilepsy; (3) what is required for prevention and cure of epilepsy; and (4) epilepsy and comorbidities, with a special focus on aging and mental health. This report provides a summary of recommendations that emerged at ERF2013 about how to (1) strengthen epilepsy research, (2) reduce the treatment gap, and (3) reduce the burden and stigma associated with epilepsy. Half of the 6 million European citizens with epilepsy feel stigmatized and experience social exclusion, stressing the need for funding trans-European awareness campaigns and monitoring their impact on stigma, in line with the global commitment of the European Commission and with the recommendations made in the 2011 Written Declaration on Epilepsy. Epilepsy care has high rates of misdiagnosis and considerable variability in organization and quality across European countries, translating into huge societal cost (0.2% GDP) and stressing the need for cost-effective programs of harmonization and optimization of epilepsy care throughout Europe. There is currently no cure or prevention for epilepsy, and 30% of affected persons are not controlled by current treatments, stressing the need for pursuing research efforts in the field within Horizon 2020. Priorities should include (1) development of innovative biomarkers and therapeutic targets and strategies, from gene and cell-based therapies to technologically advanced surgical treatment; (2) addressing issues raised by pediatric and aging populations, as well as by specific etiologies and comorbidities such as traumatic brain injury (TBI) and cognitive dysfunction, toward more personalized medicine and prevention; and (3) translational studies and clinical trials built upon well-established European consortia.

KEY WORDS: Advocacy, Biomarkers, Cure, Epileptogenesis, Epilepsy, European Commission, Horizon 2020, Research, Treatment.
The European Forum on Epilepsy Research (ERF2013) was an initiative of Epilepsy Advocacy Europe (EAE), a collaborative joint Task Force of the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). The Forum was co-funded by the European Commission’s 7th Framework Programme and hosted in conjunction with the Irish Presidency of the Council of the EU during the European Month of the Brain, providing an opportunity to move forward the agenda outlined in the Written Declaration on Epilepsy approved by the European Parliament in 2011.1 According to this declaration, 6 million European citizens have epilepsy, many of whom also have difficulties at school, high levels of unemployment, stigma, and prejudice (see Table 1).1 This declaration calls on the European commission and council to encourage research and innovation in the areas of prevention, early diagnosis and treatment of epilepsy, and in that of health impact assessments, take initiatives to encourage Member States to ensure equal quality of life for people with epilepsy, and calls on the Member States to introduce appropriate legislation to protect the rights of all people with epilepsy. To address these issues, EAE selected six main topics to be covered during the forum: (1) Epilepsy in the Developing Brain, (2) New Targets for Innovative Diagnosis and Treatments, (3) What Is Required for Prevention and Cure, (4) Epilepsy and Comorbidities—Linked to Healthy Aging and Mental Health, (5) Standards of Care, and (6) Stigma. These six topics included 27 lectures for which content and speakers were selected by the EAE and 12 appointed chairs based on experts’ position, without using a specific methodology or systematic review process. A total of 270 participants from 57 countries, including each of the 27 EU Member States, were present at the Forum. The list of speakers and government’s representatives is provided in Data S1. This report summarizes the views expressed by these participants during the forum, and does not constitute a formal consensus statement.

Stigma and the Burden of Epilepsy

Social exclusion and stigma largely contribute to the global burden of epilepsy. Stigma, which is largely caused by the lack of public awareness of the nature of the disease, is the greatest problem faced by many people with epilepsy.9 Children with epilepsy may be banned from school, adults may be barred from marriage, and employment is often denied, even when seizures do not render the work unsuitable or unsafe.3 In a study involving >6,000 adults from 10 European countries, more than half felt stigmatized, and 18% felt highly stigmatized because of their epilepsy.10 Although public attitudes toward epilepsy have improved significantly over the last 40 years,9 recent surveys indicate that, at least in some, this improvement may have slipped back.11

Need for awareness and knowledge to change perceptions

Raising public awareness and knowledge is essential to fight stigma effectively.12 Awareness should encompass the notion that some forms of epilepsy can be life-threatening, due to the risk of seizure-related injuries, status epilepticus and, in particular, sudden unexpected death in epilepsy (SUDEP). As stated in the 2012 US Institute of Medicine’s...
One specific example is the right to drive, which is an important component of a person’s quality of life, and shown to have large inconsistencies across European countries in the past. The recent EC Directive on Driving aims at promoting harmonization on this issue.

### Ensuring Adequate Standards of Care

Epilepsy is characterized by a large variety of syndromes and etiologies with different clinical manifestations and prognoses. Because of this, adequate care of people with epilepsy is dependent on the availability of diagnostic services with a high degree of expertise and, in many cases, ability to optimize complex and specialized treatments. Standards of care should be based on a network of physicians and/or services providing stepwise access to different levels of specialized expertise offering a balanced relationship between costs and patient’s benefits.

The NICE (National Institute for Health and Care Excellence) guidelines recommend that all adult and children having a first seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs (http://www.nice.org.uk/guidance/cg137/chapter/guidance#following-a-first-seizure). If initial treatment fails to control seizures, patients should be evaluated ideally at a comprehensive epilepsy center in order to reassess the diagnosis and identify the most appropriate therapeutic options.

The point prevalence of epilepsy is approximately 0.7% of the population, and up to one third of individuals with epilepsy fail to achieve sustained seizure freedom with available medications. Based on these figures, and considering that most European comprehensive epilepsy centers manage between 2,000 and 4,000 patients, at least one such center per a population of 1–2 million people should be accessible. These centers, in turn, should have access to high-resolution magnetic resonance imaging (MRI) and inpatient video–electroencephalography (EEG) long-term recording (epilepsy monitoring unit), and a multidisciplinary team that should also include neuropsychologists.
and/or psychiatrists. Genetic counselling should also be available. The possibility of recording from implanted electrodes (invasive EEG) and offering epilepsy surgery should be available in comprehensive epilepsy centers that can assemble sufficient expertise and a sufficient annual number of surgical procedures to ensure optimal performance. Although robust evidence is lacking to ascertain this number, the EU-funded E-PILEPSY pilot network of cooperation on epilepsy surgery has recently proposed to set this number to 15 resective surgeries per year. Patients should be given the opportunity to participate in high-quality clinical research where appropriate.

There seems to be considerable variability in quality of epilepsy care across countries within Europe, especially for epilepsy surgery,17–20 emphasizing the need for harmonization program and European guidelines outlining minimum standards of care.

**Identifying Priorities for Epilepsy Research**

Epilepsy in the developing brain

Epilepsies are the primary cause of neurologic morbidity in children, with 40% of incident cases of epilepsy occurring before the age of 15.21 However, the etiology of 55–75% of epilepsies remains unknown.22 Seizures in preterm and newborn babies remain the most frequent neurologic problem in neonatology intensive care units, but it is still unclear whether early seizures are the cause of long-term neurologic deficits. Studies on animal models indicate that epileptogenesis and cognitive deficits result from early seizures, but the underlying mechanisms are incompletely understood.23 The main molecular targets of current antiepileptic drugs (AEDs) also regulate developmental processes, such as cell proliferation, migration, differentiation, and physiologic apoptotic cell death.24,25 Therefore, cognitive deficits found in about 25% of children with epilepsy could also be related to adverse effects of AEDs.26 Overall, childhood epilepsies have specificities that cannot be addressed by considering them as a subset of adult epilepsies. Convergence of concepts, data, networks, and technologic and regulatory improvements have emerged in the field of pediatric epileptology during the last decade, setting the stage to address the short-, medium-, and long-term fundamental questions delineated below.

Short- and medium-term research priorities should focus on understanding mechanisms of childhood epilepsies, and more specifically include: (1) postgenomic research on developmental brain disorders with parallel studies on surgical tissue to allow investigations from bench to bedside and back; (2) studies on the causal heterogeneity and phenotypic diversity or similarity of pediatric epilepsies; (3) development of experimental models to elucidate mechanisms of epileptogenesis in the immature brain; (4) investigations of the mechanisms underlying cognitive dysfunction in age-related epileptic encephalopathies and the interference between epileptogenic networks and normal brain function; and (5) innovative trial designs to investigate therapeutic interventions in small but homogeneous populations of patients with age-related epileptic encephalopathies. Long-term research priorities should translate mechanistic knowledge into treatments, with the aim to (1) develop innovative strategies to prevent and cure childhood epilepsies and to prevent cognitive deterioration; and (2) identify age- and syndrome-specific drug targets that can be translated into drug discovery and novel trial designs.

**Novel targets for innovative diagnostics and treatment of epilepsy**

Second-generation AEDs have improved medical management by providing more treatment options—sometimes with better tolerability and safety and fewer interactions with concomitant medications than first-generation AEDs—but have failed to demonstrate superior efficacy over these older AEDs, such as valproic acid and carbamazepine.27 This likely reflects the fact that all current AEDs target neurotransmitter release or receptors and ion channels involved in regulating neuronal excitability, but not the mechanisms inherent to the pathophysiology of drug resistance and/or the disease. For a major breakthrough in epilepsy therapy, we need to identify novel drug targets that could lead to the discovery of new medications that are effective against currently drug-resistant epilepsy, or able to alter the course of the disease.28 Recent progress in understanding the mechanisms involved in epileptogenesis, seizure emergence (ictogenesis), and drug resistance holds promise for the discovery of new targets not only for better treatments, but also for innovative biomarker-based diagnostic tools.29–31

**Nonneuronal modulation of epileptic activities: glial cells and inflammatory processes**

Glial cells (astrocytes and microglia) undergo phenotypic and functional alterations in epilepsy. The emerging concept of gliotransmission and the role of astrocytes as signaling units in the so-called tripartite synapse, support the crucial contribution of glial cells to changes in neuronal function.32 New evidence from experimental models of epilepsy and different drug-resistant forms of human epilepsy shows that glial cells release neuromodulatory molecules (e.g., glutamate, ATP, cytokines), which can play an important role in seizure generation, maladaptive plasticity, and comorbidities.33 Although glial cells offer potential targets for innovative diagnostics and treatments for epilepsy, open questions about their role in seizure generation still need to be addressed, and in particular: (1) the role of glia in seizure initiation versus spread versus termination; (2) functional/phenotypic changes in glia during ictogenesis and epileptogenesis by differentiating homeostatic from deleterious
The role of glia in pharmacoresistance and high risk of adverse effects, unfeasible routes of administration, or lack of adequately powered preclinical studies. Moreover, little attention has been paid to age-specificity of mechanisms of epileptogenesis, or the presumed relevance of the animal model to the clinical situation. To address these limitations, future efforts should be targeted to do the following: (1) identify epileptogenic mechanisms for different models; (2) understanding whether combined anti-inflammatory treatments may lead to improved clinical outcomes compared to individual interventions; (3) identifying the optimal target population and modalities of intervention; and (5) searching for biomarkers of glia activation, brain inflammation, and altered blood–brain barrier function, to improve diagnosis, patients stratification, and prognosis.

Noncoding genes as therapeutic targets

About 85% of the human genome is actively transcribed as noncoding RNA, which represents a major layer of regulatory control of gene expression and a potential target for epilepsy treatments. In particular, microRNAs are a class of small noncoding RNAs with critical roles in brain development and function that could be used for therapeutic or diagnostic purposes. Indeed, the levels of several microRNAs are altered both in brain and blood by seizure activity in animal models as well as in resected human epileptic tissue. Priority research objectives in this area include the following: (1) improving our understanding of noncoding RNA in regulating gene expression in epilepsy; (2) developing methods for targeting noncoding RNAs for therapeutic benefit; (3) determining the role of variants in noncoding RNA sequences in the human genome as risk factors for epilepsy; and (4) identifying microRNAs in body fluids which could serve as molecular biomarkers of epileptogenesis.

Gene therapy and cell therapy

Gene therapy and cell therapy have gained attention as potential innovative therapeutic strategies for epilepsy. A specific potassium channel Kv1.1 and combinatorial approach of neuropeptide Y and its receptor Y2 are recent examples demonstrating the efficacy of one-time gene therapy in various chronic models of epilepsy. A combinatorial gene therapy approach with FGF-2 and brain-derived neurotrophic factor (BDNF), administered shortly after the epileptogenic insult, demonstrated that gene therapy can also exert antiepileptogenic effects. Optogenetic, coupled with gene therapy–mediated halorhodopsin (NpHR) based inhibition of excitatory neurons or ChR2 (channelrhodopsin-2) based activation of interneurons, has been shown to suppress seizure activity in various in vitro and in vivo models of epilepsy. Animal studies also suggest that stem cells derived from the patient’s own somatic cells (skin fibroblasts) or so-called induced pluripotent stem (iPS) cells, can differentiate into γ-aminobutyric acid (GABA)ergic neurons, and could be transplanted to inhibit seizures.

The main open research questions in this field relate to the optimization of the safety and efficacy of these therapies to a level appropriate for undertaking clinical trials. Directions to investigate should include (1) manipulation of RNA interference or epigenetic mechanisms, (2) overexpression of native proteins, and (3) development of closed-loop optogenetics.

Improving epilepsy surgery outcomes

Epilepsy surgery is currently the most effective treatment for patients with drug-resistant epilepsy, yet still failing in a substantial proportion of patients. Thus, we need to continue improving the performance of presurgical investigations and surgical therapies. Specific objectives to be pursued by further research include the following: (1) development of tools to better determine noninvasively the extent of the epileptogenic zone; (2) characterization of dysfunctional large brain networks, which may allow selection of candidates for other therapies such as neuromodulation; (3) development of more powerful scalp and intracranial electrodes to be used in humans; (4) development of novel surgical approaches including magnetic resonance imaging (MRI)–guided laser ablation of the epileptogenic zone and closed-loop stimulation of the nervous system.

What is required for prevention and cure?

Currently available AEDs have not been found to prevent epileptogenesis, or to alter the natural course of the disease, and their effect is essentially symptomatic. Preclinical proof-of-concept studies have revealed that about a dozen different treatments can reduce the development of epilepsy and/or its severity or development of comorbidities after brain insults such as status epilepticus or traumatic brain injury (TBI). However, many of these treatments are unlikely to proceed to clinic, for a variety of reasons such as high risk of adverse effects, unfeasible routes of administration, or lack of adequately powered preclinical studies. Moreover, little attention has been paid to age-specificity of mechanisms of epileptogenesis, or the presumed relevance of the animal model to the clinical situation. To address these limitations, future efforts should be targeted to do the following: (1) identify epileptogenic mechanisms for different epilepsy syndromes at different ages, including genes and genetic variability (application of state-of-the art bioinformatics could be used to analyze available [“omics”] data, and predict disease pathways and therapeutic targets); (2)
design tools for higher-throughput screening of novel treatments, including innovative drug screening assays, such as the genetic zebra fish models of epilepsies; (3) develop technologies for higher throughput, easier to use video–electroencephalography (EEG) monitoring and drug delivery in animal models; (4) develop age- and syndrome-relevant models for studying mechanisms of epileptogenesis and efficacy of treatments; and (5) Provide resources for validation of novel targets for both acquired and genetic epilepsies in clinically relevant animal models with clinically applicable endpoints.

Although preclinical efforts are likely to yield attractive antiepileptogenic candidate treatments, several obstacles need to be overcome for clinical translation. The main challenges include: (1) the identification of the right target population to be tested, (2) the availability of relevant biomarkers for patient stratification and prediction of treatment response, (3) the difficulty in recruiting patients into clinical trials where only a minority would be expected to develop epilepsy, and (4) the reluctance of the pharmaceutical industry to invest into an area where therapeutic benefits may take several years to be demonstrated. For instance, the risk of epilepsy after TBI, stroke, or cerebral infection varies between 3% and 50% depending on various risk factors. High-risk patients may be suitable candidates for clinical trials for antiepileptogenesis, provided that new biomarkers will allow identifying the endophenotypes associated with a higher risk of epilepsy.

Proposal for a European roadmap for translational research

Based on the above considerations, a European roadmap is proposed aimed at supporting target-driven discovery and development of antiepileptogenic drugs for prevention and cure of epilepsy. The roadmap should involve the following: (1) establishing a preclinical European Consortium for Antiepileptogenesis studies, and a clinical European Consortium for Antiepileptogenesis studies; (2) establishing a European Biomarker Consortium for identification of different endophenotypes of patients at high risk for epilepsy and disease progression (a subproject could include the establishment of a European Epilepsy database); (3) creating an academia-industry partnership to develop innovative technologies for preclinical and clinical seizure detection and drug-delivery; (4) implementing comparative preclinical and clinical proof of concept studies of antiepileptogenic drugs for prevention of epilepsy; and (5) exploring the feasibility of developing a European Epilepsy Surveillance System to monitor the epidemiology over time and thus effects of future preventive interventions.

Comorbidities of epilepsy with focus on aging and mental health

Cognitive, behavioral, and psychiatric comorbidities in epilepsy are frequent and can affect profoundly quality of life, sometimes more than the seizures per se. They often go underdiagnosed due to an overriding focus by physicians on suppressing the seizures, and may in fact be precipitated by the treatment used to control the seizures. In children and early onset epilepsies, developmental hindrance is very common, with major behavioral problems in children being autism as well as hyperactivity and attention deficit disorders. The increased incidence of autism spectrum disorders in epilepsy, compared to other chronic disorders such as asthma, diabetes, and migraine, has been interpreted as probably reflecting an epilepsy-specific comorbidity. Further research on the origin of comorbidities and their management can impact positively on the patients’ quality of life, and improve the cost-effectiveness of care to this population.

Switching focus from chronic to new-onset epilepsies

Investigations in patients with chronic epilepsy suggest that many cognitive problems may develop in the early phases of epilepsy, and that a large portion of the impairments seen in chronic epilepsy results from developmental hindrance. In fact, recent studies in large groups of untreated new-onset epilepsies demonstrate that, dependent on the type of epilepsy, cognitive impairments are present in nearly half of the patients at the time of first diagnosis. Similarly, children with new-onset epilepsies are often impaired from the beginning of the disease, and there is evidence that academic and behavioral problems in children antedate the first recognized seizure. Like cognitive impairment, psychiatric comorbidity is now considered not only a possible consequence but also a precursor of epilepsy, possibly as an expression of a common underlying brain pathology. Overall, existing evidence indicates that early and successful interventions may protect against negative cognitive development. Successful seizure control with AEDs can help to preserve cognitive capabilities and mental health, but it may also cause additional problems. Another open question is whether the comorbidities of epilepsy may accelerate mental aging and promote cognitive decline. An early epidemiologic study demonstrated a greater frequency of neurodegenerative conditions like Alzheimer’s or Parkinson’s disease in epilepsy patients compared to individuals without epilepsy.

Setting the research priorities

Priorities for future research in this area should include (1) identification of factors that lead to cognitive impairment or behavioral and psychiatric disturbances; (2) investigation of the relationship between disease development and cognitive and behavioral comorbidity, elucidating the role of the latter as a precursor as well as a consequence of seizure occurrence; (3) assessment of large cohorts of patients using multimodal and, whenever possible, longitudinal studies, coupled with detailed clinical phenotyping and appropriate omics; (4) search for metabolic, functional,
or molecular biomarkers that could allow early identification of patients at risk for the development of severe cognitive impairment; and (5) elucidation of the mechanisms responsible for AED-related cognitive impairment.

**Conclusions**

The purpose of ERF2013 was to propose a roadmap highlighting how the Written Declaration on Epilepsy, approved by the European Parliament in 2011, can be implemented in practice, and what resources are needed. A clear message was delivered to politicians and to policy makers that further funding for epilepsy research is needed within the next EU framework program (Horizon 2020). Major research priority areas discussed at the Forum (Table 2) include (1) understanding epilepsy in the developing brain; (2) identifying new targets for innovative diagnostics and treatments; (3) prevention and cure of epilepsy; and (4) understanding epileptogenesis in different settings to design innovative disease-modifying treatments.

**Acknowledgments**

We wish to thank the following colleagues and ERF 2013 participants for their contribution to the success of the Forum and their valuable input into various sections of the present report: Albert Aldenkamp (The Netherlands), Gus Baker (United Kingdom), Ettore Beghi (Italy), Christophe Bernard (France), Martin Brodie (United Kingdom), Catherine Chiron (France), Helen Cross (United Kingdom), Norman Delanty (Ireland), Paula Fernandes (Brazil), Antonio Gil-Nagel (Spain), Renzo Guerrini (Italy), Peter Halász (Hungary), Christoph Helmstaedter (Germany), David Henshall (Ireland), Gilles Huberfeld (France), Ann Jacoby (United Kingdom), Joanna Jedrzejczak (Poland), Henrik Klitgaard (Belgium), Ruediger Koehl (Germany), Merab Kokaia (Sweden), Hana Kubova (Czech Republic), Dimitri Kullman (United Kingdom), Holger Lerche (Germany), Heiko Luhmann (Germany), Andrey Mazarati (U.S.A.), Solomon L. Moshé (U.S.A.), Alfonso Represa (France), Ley Sander (United Kingdom), Raman Sankar (U.S.A.), Dieter Schmidt (Germany), Margitta Seec (Switzerland), Kevin J Staley (U.S.A.), Maria Thom (United Kingdom), Torbjörn Tomson (Sweden), Patrick Van Bogaert (Belgium), and Annamaria Vezzani (Italy).

**Epilepsia, 56(11):1687–1695, 2015**

doi: 10.1111/epi.13201
DISCLOSURE OF CONFLICTS OF INTEREST

This report was written by experts selected by the International League Against Epilepsy (ILAE) and by the International Bureau for Epilepsy (IBE) and was approved for publication by the ILAE and IBE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE and IBE.

M. Baulac received grants from the French Ministry for Research, and speaker’s or consultancy fees from Eisai, GlaxoSmithKline, UCB Pharma, and Viropharma. H. de Boer received consultancy fees from UCB Pharma. CE Elger received grants from the Deutsche Forschungsgemeinschaft, and speaker’s or consultancy fees from Bial, Cyberonics, Desitin, Eisai, Medtronic, and Novartis. R. Källiväinen received grants from the Academy of Finland and Vaajasalo Foundation, and consulting or speaker fees from UCB Pharma, Eisai, Orion, Fenomedical, Medtronic, GlaxoSmithKline, and Pfizer. J. Mifsud received grants from the European Union, United Nations Educational, Scientific and Cultural Organization, and the University of Malta. She also received speaker’s or consultancy fees from GlaxoSmithKline and Viropharma. E. Perucca received grants from the European Union, the Italian Medicines Agency, the Italian Ministry of Health, and the C. Mondino National Neurological Institute. He also received speaker’s or consultancy fees from Eisai, GlaxoSmithKline, GW Pharma, Institution de Lavigny, Medicem, Ranbaxy, UCB Pharma, Upsher-Smith, and Viropharma. P. Ryvlin received consulting or speaker’s fees from UCB Pharma, Eisai, GlaxoSmithKline, and Cyberonics. A. Pitkanen received research grants from the Academy of Finland, The Sigrid Juselius Foundation, CURE (Citizens United for Research in Epilepsy), and EU FP7 (EPITARGET). Other authors have no conflicts to disclose. We confirm that we have read the Journal’s policy on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Data S1.** List of participants to the European Forum on Epilepsy Research, including members of the organizing and advisory committees, national contact points, and speakers.