Harmonization in preclinical epilepsy research: A joint AES/ILAE translational initiative

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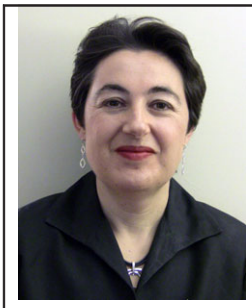

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Summary

Among the priority next steps outlined during the first translational epilepsy research workshop in London, United Kingdom (2012), jointly organized by the American Epilepsy Society (AES) and the International League Against Epilepsy (ILAE), are the harmonization of research practices used in preclinical studies and the development of infrastructure that facilitates multicenter preclinical studies. The AES/ILAE Translational Task Force of the ILAE has been pursuing initiatives that advance these goals. In this supplement, we present the first reports of the working groups of the Task Force that aim to improve practices of performing rodent video–electroencephalography (vEEG) studies in experimental controls, generate systematic reviews of preclinical research data, and develop preclinical common data elements (CDEs) for epilepsy research in animals.

KEY WORDS: Preclinical research, Electroencephalography, Common data elements, Epilepsy, Systematic review, Rodent.

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Following the first international translational workshop on optimizing preclinical epilepsy in London (2012), jointly organized by the American Epilepsy Society (AES) and the International League Against Epilepsy (ILAE),[1] a number of priority steps were recognized as important to undertake. Among these, defining and harmonizing best research practices and building an infrastructure to facilitate data comparisons and sharing for animal studies were thought to be an important step to accelerate and optimize preclinical epilepsy research. To implement these efforts, the AES and ILAE appointed the AES/ILAE Translational Task Force (TF), co-chaired by Jacqueline French (AES), Aristea Galanopoulou (AES), Terence O'Brien (ILAE), and Michele Simonato (ILAE). The members of the TF were also jointly appointed by the AES (Amy Brooks-Kayal, Frances Jensen, and Helen Scharfman) and ILAE (Marco De Curtis, Akio Ikeda, and Asla Pitkänen), whereas Solomon (Nico) Moshé acted as liaison to the executive committee of the ILAE. The first tasks agreed upon were the harmonization of rodent video-electroencephalography (vEEG) and electrophysiologic studies in rodents (TASK1; co-led by Drs. Galanopoulou, De Curtis, and Ikeda), systematic reviews of animal model data (TASK2; co-led by Drs Simonato, Brooks-Kayal, and Jensen), creation of preclinical common data elements for epilepsy research (TASK3; co-led by Drs. Scharfman, French, and Pitkänen), and development of infrastructure for multicenter preclinical studies (TASK4; co-led by Drs. O'Brien, Ikeda, and Moshé). Following an open call for volunteers, each TASK formed working groups (WGs). The first reports of their work appear in this supplement.

The TASK1-WGs address the technological, methodological aspects, and interpretation of electrophysiologic studies, done in experimental controls. Unlike human EEG studies, where there is a standardized way of performing the studies and their interpretation follows widely accepted standards and norms, EEG studies in rodents are done using different types and placements of electrodes and different acquisition and analysis methods, and their interpretation varies across labs and investigators. In exploratory studies, the diversity in methods and definitions is often dictated by the experimental goals of each study. However, in preclinical studies aiming to ultimately deliver a new treatment, diagnostic tool, or biomarker to the clinics, harmonization of the procedures followed to perform or interpret EEG or in vitro electrophysiologic studies is essential to allow across study comparisons and cross-validation, minimize the failures to replicate, and effectively translate the findings to humans, when tested in the clinics. Currently, there is no organized method of determining a normal background in rodent EEG studies, no uniform agreement on what is an electrographic seizure, and no system of classifying seizures or other EEG and electrophysiologic abnormalities in rodents. As a first step, the goal of each of the first TASK1-WGs was to evaluate and propose methodologic standards for performing and interpreting electrophysiologic studies in rodents used as experimental controls. The description, definition, terminology, and classification of the abnormal patterns will be done in the future. Early discussions among the TASK1-WG members agreed that the term "normal" is difficult to define in rodents because there is no prior comprehensive evaluation for neurologic or other medical disorders, and these animals are exposed to invasive surgeries to place EEG electrodes. As a result, these first TF reports utilize the term "controls" to denote animals that have not had exposure to the specific experimental interventions or settings tested in the respective studies, and to prompt the investigators to handle and evaluate these controls with the same protocols as the animals allocated to the other experimental groups. In this supplement, the following TASK1 reports are included. The TASK1-WG1 group reports on best practices pertaining to studies using surface or epi-/subdural EEG in adult rodent controls.[2] The TASK1-WG3 group addresses the methodologies and interpretation of depth electrophysiologic in studies in vivo in adult rodent controls,[3] whereas the TASK1-WG4 group focuses on in vitro electrophysiologic studies.[4] The TASK1-WG5 group proposes standards for data acquisition and analysis for the electrophysiologic recordings.[5] Among the future goals of the TF will be to propose an agreement on terminology and classification of abnormal vEEG and electrophysiologic patterns and behaviors, similar to the classification systems that exist for humans.

The goal of the TASK2 group is to organize systematic reviews on various topics important for the preclinical epilepsy research studies. This is an effort done through a collaboration with CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) (http://www.dcn.ed.ac.uk/camarades/default.htm). Electronic citation repositories allow access to large amounts of articles that cannot be examined by a single individual. Moreover, the statistical power of single basic and preclinical studies is often insufficient to draw solid conclusions. One approach to address these problems (well established in clinical research) is the use of systematic reviews of the literature and meta-analysis of the data. The idea of TASK2 is to apply these techniques to preclinical epilepsy studies. There are of course many topics in preclinical epilepsy research that are worthy of systematic reviews and meta-analysis. The first selected topic was the identification and characterization of outcome measures used in animal models of epilepsy.[6] This broad analysis is expected to provide evidence to inform attempts to improve the currently available models of chronic epilepsy. Future goals will be to analyze the effects in epilepsy models of U.S. Food and Drug Administration (FDA)– and European Medicines Agency (EMA)–approved drugs, using the same approach. The TASK2 report outlines the objectives, search strategy, selection criteria, and methods for the statistical analyses used in this project.

It is widely believed that harmonization of research methodology and reporting will speed the evaluation of translational therapies. Without methodology to allow labs to perform experiments in similar fashion, or indeed without availability of reporting mechanisms to determine whether there were important differences in execution, it is very difficult to accurately interpret results. Following the experience of the clinical common data elements (CDEs) (https://www.commondataelements.ninds.nih.gov/default.aspx#page=Default) proposed by the National Institute of Neurological Disorders and Stroke (NINDS), which have transformed the way clinical trials are being performed and reported, the TASK3 group, in collaboration with the NINDS (Drs Brandy Fureman and Vicky Whittemore), formed several WGs tasked with the creation of preclinical CDEs and case report forms (CRFs) to be used in animal studies. These include core CDEs/CRFs or CDEs/CRFs for assessing behavior, physiologic measures and outcomes, vEEG studies, or for performing pharmacologic studies in rodents. The TASK3 report[7] presents an overview of the purpose and utility of these CDEs/CRFs in optimizing data collection and facilitating collaborative studies and data sharing. It is also an introduction to the future detailed reports of the TASK3-WGs, which will present these epilepsy CDEs/CRFs.

These first reports present the first steps of the ongoing translational initiatives, with the hope that these will be useful in facilitating the harmonization of preclinical studies in epilepsy research. This will be essential for the successful implementation of large multicenter preclinical trials, which aim to provide higher level preclinical evidence to "de-risk" clinical trials, in particular for potential antiepileptogenic/disease therapies. The authors welcome feedback from the community, as it will be essential to finetune and improve the current and future products of our TF.

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Disclosure of Conflict of Interest

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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