

The present and future utility of current screening models for AED development: What do they tell us about efficacy, tolerability, and mechanism of action of an investigation AED?

Since 1993, 13 new antiepileptic drugs have been brought to the world-wide market for the symptomatic treatment of epilepsy. Moreover, there are a number of investigational drugs currently in clinical development that will likely be available over the next 1-3 years. All of these drugs have been developed on the basis of their ability to block seizures in one or more animal seizure or epilepsy models employed by programs such as the NINDS, NIH Anticonvulsant Screening Project (ASP).¹ Each new AED that comes to the market provides the patient with another option for the treatment of their seizure disorder; however, despite the apparent success of the current discovery process, a significant need persists for those patients whose seizures remain refractory to the currently available AEDs. One advantage of the current approach is that all of the currently available AEDs have been identified on the basis of their activity in one or more of the standard models, irrespective of their molecular mechanism of action. Furthermore, they have been successful in bringing mechanistically novel AEDs to the market; i.e., the 2 ligands gabapentin and pregabalin, the SV2A ligand levetiracetam, and the functionalized amino acid derivative lacosamide. Depending on the molecular target, an in vivo screening program can be designed that will facilitate lead optimization of CNS penetrant AEDs. For example, Na⁺ channel modulators would be expected to be active in the maximal electroshock model; whereas SV2A ligands would best be identified using the kindling model of partial epilepsy. Some would argue that the current models can be used to predict CNS adverse events; however, this is not likely given the complexity of the human brain relative to that of the rodent. Having said this, the rodent behavioral assays can be useful for optimizing a series of structurally related AEDs and selecting an IND candidate. Discussion will focus on the current process employed by the Anticonvulsant Drug Development Program at the University of Utah in collaboration with the NINDS ASP and other laboratories working towards the common goal of discovering better therapeutic options for patients living with epilepsy. The presentation will also include a brief overview of the inherent advantages and limitations of the primary animal models employed in the search for new antiepileptic drugs, while offering insight into potential future directions as we seek to better understand the pathophysiology underlying acquired epilepsy, therapy resistance, and epileptogenesis.