



## Review article

## Antiepileptic drugs in development pipeline: A recent update



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## ARTICLE INFO

## Article history:

Received 16 September 2015

Received in revised form 16 April 2016

Accepted 15 June 2016

Available online 17 June 2016

## Keywords:

Seizures  
Epilepsy  
Drug development  
Neuroprotection  
Clinical trial  
Antiepileptic

## ABSTRACT

Epilepsy is the most common neurological disorder which significantly affects the quality of life and poses a health as well as economic burden on society. Epilepsy affects approximately 70 million people in the world. The present article reviews the scientific rationale, brief pathophysiology of epilepsy and newer antiepileptic drugs which are presently under clinical development. We have searched the investigational drugs using the key words 'antiepileptic drugs,' 'epilepsy,' 'Phase I,' 'Phase II' and 'Phase III' in American clinical trial registers ([clinicaltrials.gov](http://clinicaltrials.gov)), the relevant published articles using National Library of Medicine's PubMed database, company websites and supplemented results with a manual search of cross-references and conference abstracts. This review provides a brief description about the antiepileptic drugs which are targeting different mechanisms and the clinical development status of these drugs. Besides the presence of old as well as new AEDs, still there is a need of new drugs or the modified version of old drugs in order to make affected people free of seizures. An optimistic approach should be used to translate the success of preclinical testing to clinical practice. There is an urgent need to improve animal models and to explore new targets with better understanding in order to develop the novel drugs with more efficacy and safety.

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**1. Introduction**

Epilepsy is the most common neurological disorder which significantly affects the quality of life and poses a health as well as economic burden on society. Epilepsy affects an approximately 70 million people in the world [72]. In the United States, more than 300,000 people with epilepsy are younger than 14 and more than 500,000 are older than 65. With age, the incidence rate of epilepsy is fluctuating as high levels in childhood followed by decreasing order in early adult life which precedes by second high rate at the age of more than 65 years old [62]. Epilepsy diminishes health related quality of people as there is increased risk of injuries during seizures and higher mortality as compared to normal people. Epilepsy affects an estimated 1.5 million women in the United States [77]. The estimation of the corresponding rates is higher in low and middle income countries [72]. In India, the prevalence of epilepsy is 6–10 per 1000 people [92]. Sudden unexpected death in epilepsy (SUDEP) is the most common and important cause of death which is directly related to epilepsy and is the major cause of mortality in chronic uncontrolled epileptic patients [102]. With the help of new and improved approaches, many new AEDs and modified version of older drugs have been available to treat epilepsy. Of these new AEDs, few are rarely prescribed because of their serious side effects.

Despite availability of several AEDs, one-third of patients still have intolerable condition. Currently there is an urgent need to create new opportunities and improve the existing drugs to relieve patients. A review was conducted to find articles reporting on antiepileptic drugs which are under developmental phase in partial onset seizures, refractory partial seizures, generalized tonic clonic seizures, and resistant partial onset seizures in the year of 2015 and 2016. A literature search using the keywords seizures, epilepsy, drug development, clinical trials, and antiepileptic has been accomplished. Multiple databases were searched including [ClinicalTrials.gov](http://ClinicalTrials.gov), Pubmed, database, company websites and supplemented results with a manual search of cross-references and

conference abstracts. This review covers briefly introduction, pathophysiology and recent ongoing clinical trials of epilepsy.

**2. Pathophysiology**

In 2015, according to ILAE the conceptual definition of seizures or epilepsy includes “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” and epilepsy as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition”. For this, at least one episode of epilepsy is needed. The ILAE and the international Bureau for epilepsy (IBE) in 2014 have advised to regard epilepsy as a disease. The new clinical definition of epilepsy as a disease includes one of the following: (A) at least two unprovoked (or reflex) seizures occurring more than 24 h apart; or (B) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (C) diagnosis of an epilepsy syndrome [86] (Fig. 1). The hyper synchronous, abnormal discharge of neurons begins in discrete region of cortex and then spread to neighbouring regions. These activated neurons emit excessive bursts of action potential or electrical energy. The pathophysiology of epilepsy involves conversion of a normal network into a hyper excitable network. It is associated with a group of processes which disturb extracellular ion homeostasis, alter energy metabolism, change receptor function and alter transmitter uptake. In CNS, the brain consists of nerve cells and these nerve cells communicate and interact with each other through axons by discharging tiny electrical impulses. The brain along with nerve cells works on the phenomenon of electricity. The output of these electrical impulses is the release of chemicals called neurotransmitters from the axon end which in turn interacts with the next cell. These chemicals (neurotransmitters) can be excitatory or



Fig. 1. Epilepsy classification.

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