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Review article

Antiepileptic drugs in development pipeline: A recent update

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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), 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 ClinicalTrial.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.

inhibitory. The balance of these excitatory and inhibitory impulses is very important to maintain the action potential of neurons [36,62]. Release of excessive excitatory glutamate overactivates NMDA receptors resulting in excessive influx of Ca^{2+} ions. The overflow of Ca^{2+} levels caused deteriorate condition which activates cytoplasmic proteases (such as calpain I), which proteolysis cytoskeletal and other proteins [100], neuronal nitric oxide synthase (nNOS), which increases nitric oxide production in turn generating the free radical peroxynitrite that damages DNA [31] which ultimately lead to neuronal cell death (Fig. 2).

3. Antiepileptic drugs under clinical development

During the last three decades, the antiepileptic drug development has been focused on the specific therapeutic targets concerning the neurobiology of epilepsy but most of the available AEDs have not shown efficacy in treatment of patients with refractory epilepsy. Despite the apparent success of the AED discovery process, there is a need of developing more efficacious and safe antiepileptic drugs particularly for the treatment of refractory seizures. The primary goal of newer AED research should be to develop novel compounds for controlling seizures with more therapeutic efficacy and less adverse effects. Three main strategies are currently adopted by the researchers and pharmaceutical industry in order to develop novel compounds for treatment of epilepsy: (a) modification of existing drugs, (b) development of compounds against novel therapeutic targets or new hypothesis, and (c) non-mechanism based drug screening in conventional and newer animal models [81,93]. Few of newer drugs which are presently under the clinical development phases (Table 1) are discussed below.

3.1. Seletracetam and brivaracetam

The modification of the levetiracetam led to the development of the compounds, seletracetam and brivaracetam, which have greater affinity towards SV2A [57]. Seletracetam is a structural analogue of the levetiracetam, sharing the same mechanism of action by binding to synaptic vesicle protein 2A (SV2A). It possesses a 10-fold greater affinity towards SV2A which is further involved in synaptic neurotransmitter release [68]. Like levetiracetam, seletracetam did not show any anticonvulsant activity in the two classical screening models for AEDs: the maximal electroshock test (MES) and the pentylenetetrazol (PTZ) test [71]. However, it showed potent activity in other animal models of partial (kindled models) and generalized epilepsy (audiogenic seizures and genetic absence epilepsy rats from Strasbourg) [24]. On the other side, brivaracetam also possesses sodium channel blocking property which may account for its activity in other preclinical screening models, including MES and PTZ seizure models [70]. In placebo controlled Phase II trials, both brivaracetam and seletracetam have found to be effective in patients with photosensitive epilepsy [25,56]. Positive results from stage III trials implicated that brivaracetam at the dose of 50 mg when compared to 5 mg/day and 20 mg/day [28] and at the dose of 100 mg/day as compared to 20 mg/day and 50 mg/day [89] significantly improved seizure frequency in adults (16 to 70 years) with uncontrolled partial onset seizures and adjunctive brivaracetam in adults with uncontrolled focal and generalized seizures [61] along with evidence that it is around 10 times more potent for the prevention of certain types of seizure in mouse models than levetiracetam, of which it is an analogue [71].

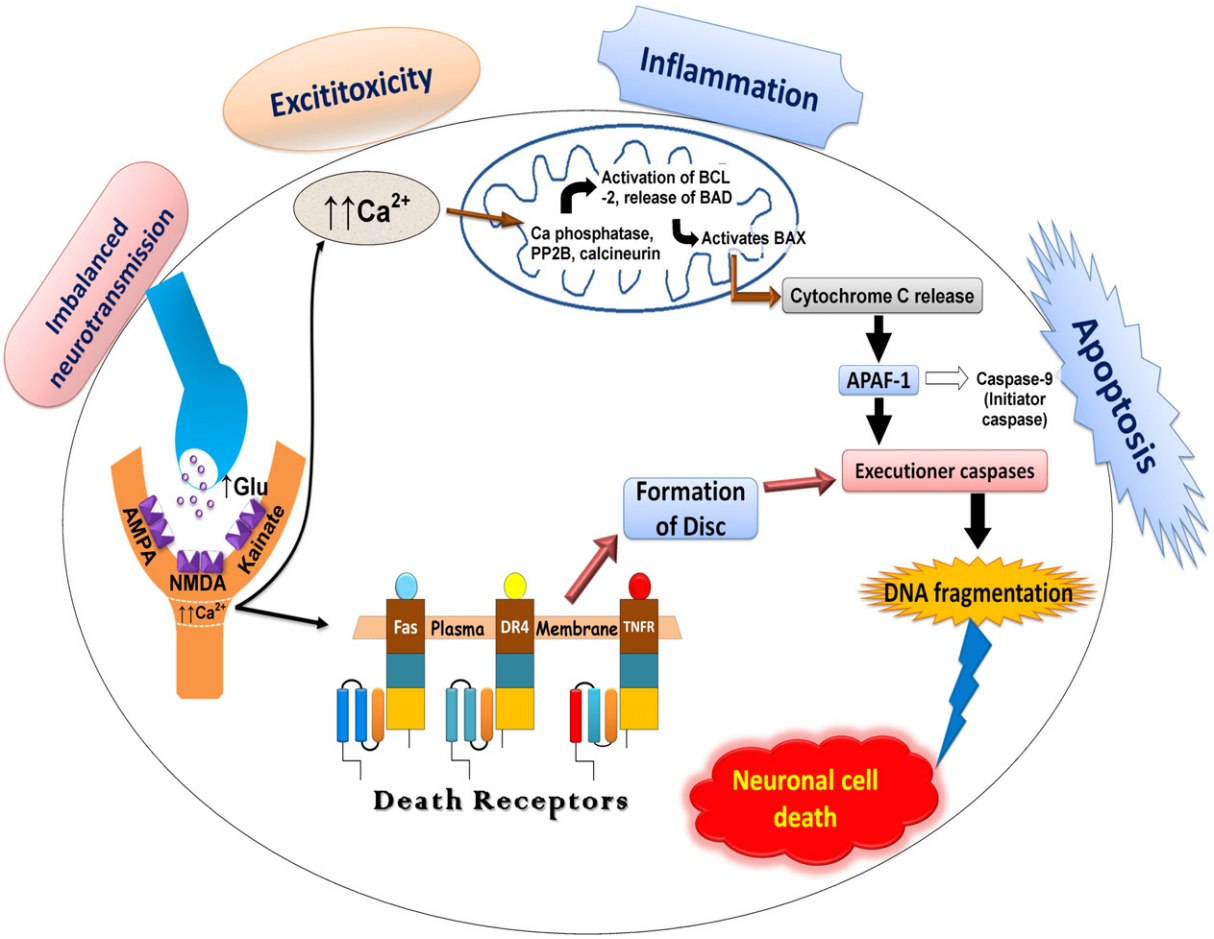
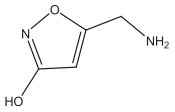
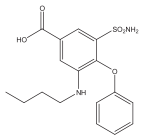
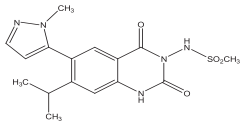
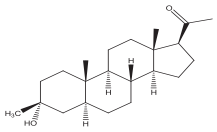
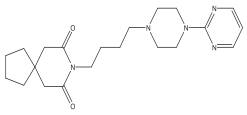
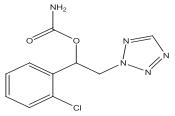
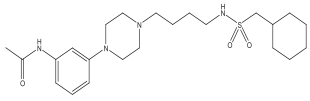
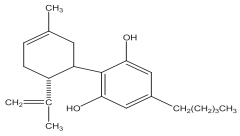
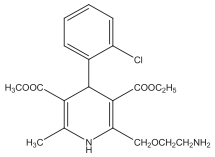
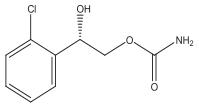
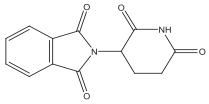
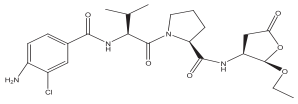
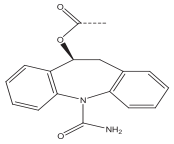


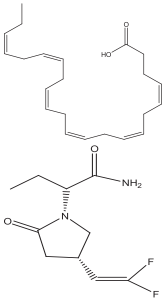
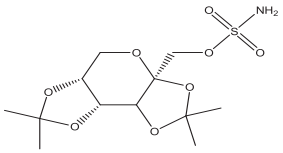
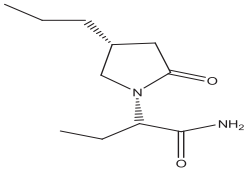
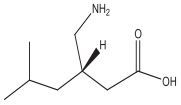
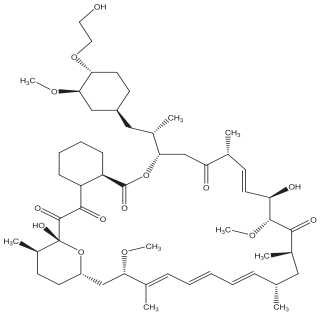
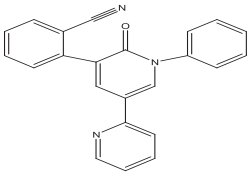
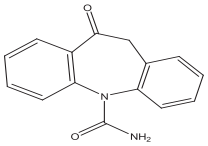
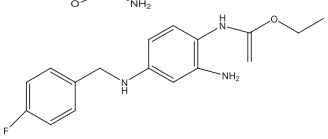
Fig. 2. Basic cascade events of pathophysiology of epilepsy.

Table 1
Current developmental status of new drugs for treatment of epilepsy.

S. no.	Name of intervention	Sponsor	Structure	Therapeutic target	Condition	Clinical development phase
1	Muscimol	National Institute of Neurological Disorders and Stroke (NINDS)		$GABA_A$ receptor	Epilepsy	Phase 1
2	Bumetanide	–		NKCC1 inhibition	Neonatal seizures	Phase 1
3	BGG492 (Selurampanel)	Novartis Pharmaceuticals		AMPA/kainate receptor antagonism	Refractory partial seizures	Phase 2
4	Ganaxolone	Marinus Pharmaceuticals		Positive allosteric modulator of $GABA_A$ receptors	Uncontrolled partial epilepsy; catamenial epilepsy	Phase 2
5	Buspirone	NINDS		5-$HT1_A$ receptor partial agonist	Localized epilepsy	Phase 2
6	YKP3089	SK Life Sciences		Sodium channel modulation, ↑ GABA release	Resistant partial onset seizures	Phase 2
7	PRX-00023	NINDS		5-HT receptors	TLE; partial epilepsy	Phase 2
8	GWP42003-P (Cannabidiol)	GW Research Ltd. INSYS Therapeutics Inc.		–	Dravet syndrome Lennox Gastaut syndrome Myoclonic epilepsy	Phase 2 Phase 3
9	Verapamil	Beverly S. Wical, Gillette Children's Specialty Healthcare		Calcium channel modulation	Dravet syndrome	Phase 2
10	RWJ-333369 (carisbamate)	SK Life Science		Not elucidated	Partial epilepsy	Phase 3
11	Thalidomide	National Institute of Neurology and Neurosurgery, Mexico			Refractory epilepsy	Phase 2
12	VX-765	Vertex Pharmaceuticals		Caspase-1 inhibitor	Resistant partial epilepsy	Phase 2
13	Eslicarbazepine acetate	Sunovion Pharmaceuticals Inc. Bial-Portela USA		Sodium channel inhibition	Epilepsy with partial onset seizures Refractory partial seizures	Phase 3
14	Docosahexaenoic acid	Canadian College of Naturopathic Medicine (CCNM)			Refractory Seizures	Phase 3

(continued on next page)

Table 1 (*continued*)

S. no.	Name of intervention	Sponsor	Structure	Therapeutic target	Condition	Clinical development phase
15	Seletracetam (ucb 44212)	UCB, Inc.		SV2A; presynaptic calcium channels inhibition	Partial onset seizures	Phase 3
16	USL255	Upsher-Smith Laboratories		Sodium and calcium channels modulation	Refractory partial-onset seizures	Phase 3
17	Brivaracetam (ucb 34714)	UCB Inc.		Same as of levetiracetam	Epilepsy	Phase 3
18	Pregabalin	Pfizer		Calcium channel modulation	Partial onset seizures; primary GTC seizures	Phase 3
19	RAD001 (Everolimus)	Novartis Pharmaceuticals Baylor College of Medicine New York University School of Medicine		mTOR inhibition	Tuberous sclerosis complex-associated refractory seizures	Phase 3
20	E2007 (Perampanel)	Eisai Inc.		Non-competitive AMPA antagonism	Refractory partial seizures; primary generalized tonic clonic seizures	Phase 3
21	TRI476	Novartis Pharmaceuticals		Sodium channel modulation	Partial onset seizures	Phase 3
22	Retigabine/ezogabine	GlaxoSmithKline		Potassium channel modulation	Partial onset refractory seizures	Phases 3, 4

Recently, brivaracetam was approved on Jan 14, 2016 by European Medicine Agency (EMA) and on Feb 18, 2016 by the U.S. Food and Drug Administration (FDA). It was approved under the trade name Briviact (developed and marketed by UCB) as an add-on treatment to other medications to treat partial onset seizures in patients age 16 years and older with epilepsy. Briviact is available in three formulations, including film-coated tablets, oral solution and solution for injection/infusion [1].

3.2. Bumetanide

Bumetanide is an inhibitor of Na-K-Cl cotransporter (NKCC). Two isoforms of NKCC are present in the body: NKCC1 is expressed in the brain and NKCC2 is present in the kidney. It has a potential use in patients with temporal lobe epilepsy having defective chloride homeostasis which is caused by increased NKCC1 expression and depolarizing GABA responses [55]. There is evidence that bumetanide application suppressed the seizure-like activity in human TLE slices through GABAergic responses [53]. Bumetanide administration in patients with temporal lobe epilepsy caused a significant reduction in number of seizures and epileptiform discharges in brain [42]. A pilot study is already underway to explore the pharmacokinetic and safety profile of bumetanide in newborns with refractory seizures [80,37].

3.3. BGG492 (Selurampanel)

The novel idea of AMPA-glutamate receptor antagonism has gained a considerable interest for the development of new antiepileptic drugs targeting this novel mechanism of action. BGG492 (Selurampanel) is an orally active competitive AMPA antagonist. It has good oral bioavailability and blood–brain barrier penetration [46]. In preclinical development, BGG492 has shown anticonvulsant activity in several rodent models of epilepsy including maximal electroshock seizure, audiogenic seizure, amygdala kindling model, and genetic models [51,58]. BGG-492 is currently in Phase II development for the treatment of patients (Table 1) with partial epilepsy [38].

3.4. Ganaxolone

Ganaxolone is the only neurosteroid in clinical development for treatment of partial onset seizures. It possesses GABA modulatory activity via acting through $GABA_A$ receptors. Several Phase II studies have been conducted in adults and pediatric patients with partial-onset seizures, refractory epilepsy and infantile spasms [26,79,9]. It was also found to be safe and effective as adjunctive therapy in adults with partial seizures [8,74]. Ganaxolone is currently in Phase III development for epilepsy (Table 1).

3.5. YKP3089

YKP-3089 is a novel compound showing a broad spectrum of efficacy in various animal models of seizures and epilepsy [26]. It is well tolerated and showed to be effective in patients with photosensitive epilepsy [41]. A Phase IIb Trial of YKP3089 is ongoing in patients with partial onset seizures [4,27].

3.6. PRX-00023

PRX-0023 (Naluzotan) is a serotonergic drug which acts via 5-HT1_A receptor. Currently, the researchers are investigating the effects of the experimental medication PRX-00023 on seizure frequency in patients with focal epilepsy [85].

3.7. GWP42003-P (Cannabidiol)

GWP42003-P (Cannabidiol) is a biologically active compound obtained from cannabis plant. Recently, this compound is being investigated for treatment of epilepsy. A Phase II study of safety and pharmacokinetics of multiple doses of GWP42003-P compared with placebo in children with Dravet syndrome has been completed in 2015 but results not posted yet [3]. Phase III trials have been initiated to explore the efficacy and safety of Cannabidiol (GWP42003P) in children and young adults with Dravet syndromes [22,23,16] and in children and young adults with Dravet or Lennox Gastaut syndromes [19,17]. Phase 3 study of long-term safety and efficacy of Cannabidiol Oral Solution as adjunctive therapy for pediatric and adult subjects with treatment resistant seizure disorders, including Lennox Gastaut syndrome (LGS) or Dravet syndrome (DS) is going on. These studies will be approximately completed in 2016 and 2017.

3.8. RWJ-333369 (carisbamate)

Carisbamate (RWJ-333369) is a novel neuromodulator drug and is currently under the clinical development for the treatment of epilepsy. It has shown the efficacy and tolerability in a Phase II clinical trial in patients with epilepsy [45,73]. 3 Phase III clinical trials of carisbamate as treatment in partial onset seizures have been completed. Among them only one randomized double blind Phase III study showed significant positive efficacy outcome at the dose of 400 mg/day in adults with refractory partial onset seizures [50,94,14,15,12].

3.9. Thalidomide

Thalidomide has shown strong anticonvulsant properties in various animal models of epilepsy. In an open label study, it has shown strong therapeutic efficacy in patients with refractory epilepsy [76].

3.10. VX-765

VX-765 (Belnacasan) is an oral compound that inhibits Caspase-1 which is involved in IL-1beta production and a wide range of immune and inflammatory processes. It is found to be effective in animal models of both acute and chronic partial seizures [69]. In Phase II study of clinical development, VX765 has been found to be well tolerated, safe and efficacious (Table 1) in treatment of patients with drug-resistant partial onset epilepsy [99].

3.11. Eslicarbazepine acetate

Eslicarbazepine acetate is a new compound with anticonvulsant activity whose mechanism of action is by blocking the voltage-gated sodium channel. In 2013, eslicarbazepine acetate under the trade name of Aptiom was approved by the U.S. Food and Drug Administration (FDA), an antiepileptic drug (AED), for use as adjunctive treatment of partial-onset seizures with or without secondary generalization, developed by Sunovion Pharmaceuticals Inc. (Sunovion). The efficacy and safety of eslicarbazepine acetate (BIA 2–093) as monotherapy are being investigated in patients with newly diagnosed partial-onset seizures [40]. In Phase III double blind, randomized, multicentre study in subjects with partial seizures which were not controlled by current AEDs, ESL as monotherapy showed effective results as significantly improved seizure outcome and well tolerated [54,95]. ESL as monotherapy long term Phase III study in subjects with partial onset seizures and similarly a Phase III study of ESL as adjunctive therapy for refractory partial seizures are going and will be completed in 2016 [39,44,91]. Results of a one year ESLIBASE retrospective study have revealed that eslicarbazepine acetate was well tolerated and effective in patients with focal seizures [105].

3.12. Retigabine/ezogabine

Retigabine has been shown to be a novel AED that acts by a unique mechanism, activating potassium channels and GABA receptors [67]. Retigabine has shown efficacy in several animal models of epilepsy [84]. The safety and efficacy of retigabine have been evaluated in Phase III studies in refractory epilepsy patients with partial-onset seizures and were found to be well tolerated and efficacious as adjunctive therapy in these groups of patients [29,82]. Currently, a multicentric, long-term, Phase III study is ongoing to assess the long-term safety, tolerability and efficacy of retigabine immediate-release (IR) as adjunctive

therapy (Table 1) in treatment of patients with drug-resistant partial-onset seizures, results are expected during 2016 [5].

Retigabine is also in Phase IV trial to examine its effect on urinary voiding function in subjects with partial onset seizures in addition to existing anti-epileptic drugs [20]. A Phase IV adjunctive treatment dose optimization study evaluating the efficacy, safety, and health outcomes of ezogabine/retigabine immediate release (IR) (GW582892) in adult subjects with partial onset seizures (POS) was terminated in 2013 after enrolling 6 subjects as decision was taken by sponsor (GlaxoSmithkline) [64]. GSK considered the early adjunctive treatment study population is irrelevant after reassessing the benefit and risk profile of retigabine [35]. Apart from this, one more Phase II study of pharmacokinetics, safety and tolerability of ezogabine/retigabine in subjects aged 12 years to less than 18 years with uncontrolled partial onset seizures or Lennox Gastaut syndrome was terminated as warned by FDA [98].

3.13. Docosahexaenoic acid

Omega-3 polyunsaturated fatty acids (PUFAs) are dietary fatty acids that are involved in several physiological processes of brain. Docosahexaenoic acid (DHA) which is an omega-3 fatty acid has been found to increase seizure thresholds in animals [101]. Subcutaneous administration of DHA increased the resistance to seizures in rodent PTZ model of epilepsy [103]. A double blind placebo controlled Phase II trial is ongoing to evaluate the effects of DHA in fish oil for the treatment of seizure disorders [34].

3.14. USL255

Topiramate Immediate Release (TPM-IR) is a broad-spectrum, well-established AED with multiple mechanisms of action including $GABA_A$ agonist, glutamate antagonist, and sodium channel antagonist [83]. TPM-IR is approved in many countries as an adjunctive treatment for patients with partial-onset seizures or primary generalized tonic–clonic seizures. USL255 is an extended release topiramate (TPM-XR) formulation that was developed to deliver consistent drug release over a 24 h dosing interval [33]. A double-blind, randomized, placebo controlled PREVAIL Phase III clinical study (Table 1) demonstrated that once-daily administration of USL255 is an effective adjunctive therapy for reducing the seizure frequency in patients with refractory partial onset seizures [32].

3.15. Pregabalin

Pregabalin is one of the newer antiepileptic drugs developed for the treatment of partial epilepsy. The primary mechanism of action of pregabalin is the inhibition of depolarization at voltage gated calcium channels resulting in decreased release of excitatory neurotransmitters (glutamate) at nerve terminals [90]. It showed a potent anticonvulsant activity in various experimental models of seizures and epilepsy such as maximal electroshock (MES), pentylenetetrazol induced seizures, audiogenic seizures in genetically seizure susceptible DBA/2 mice and kindled seizure in rats [65,106]. The results of three randomized placebo controlled trials indicate that pregabalin is highly effective in the treatment of patients with partial seizures with or without secondary generalization [30]. The efficacy and safety of pregabalin as an add-on therapy in treatment of refractory partial epilepsy have been evaluated in six randomized, placebo-controlled trials involving 2009 participants. It was found to be significantly effective in reducing seizure frequency and increasing seizure freedom rates in patients with drug-resistant partial epilepsy [66]. Currently, four Phase III, double-blind, placebo-controlled, multicentric studies are ongoing in order to assess the efficacy and safety of pregabalin as adjunctive therapy in pediatric patients (Table 1) with partial onset seizures and in pediatric and adult subjects with primary generalized tonic clonic seizures which are estimated to be completed in 2016, 2017 and 2018 respectively [13,11,2,10].

3.16. RAD001 (Everolimus)

Everolimus is a mammalian target of rapamycin (mTOR) complex 1 inhibitor with demonstrated benefit in several manifestations of tuberous sclerosis complex. In a multicentric, open-label, Phase II clinical trial, Everolimus treatment demonstrated a significant reduction in the frequency as well as duration of seizures in TSC refractory epilepsy patients [60]. A Phase II study of adjunctive Everolimus (RAD 001) therapy for epilepsy in children with Sturge–Weber Syndrome is going on and expected to be completed in 2018 [18]. Another Phase II study to measure effect of Everolimus on mTOR signaling in patients with tuberous sclerosis complex (TSC) and Focal Cortical Dysplasia (FCD) is going on with estimated enrollment of 30 patients is currently going on and will be finished in 2017 [6]. The safety and efficacy of two trough ranges of Everolimus as adjunctive therapy in a randomized, placebo-controlled Phase III study in TSC patients with refractory partial-onset seizures have been completed and results are expected during 2016 [7].

3.17. E2007 (Perampanel)

E2007 (Perampanel) is an orally administered, highly selective non-competitive AMPA-glutamate receptor antagonist, discovered and under development by Eisai Laboratories [52]. Perampanel has shown a broad spectrum of activity in several animal models of epilepsy including MES seizure, PTZ induced seizures, audiogenic seizures and amygdala kindled model of epilepsy [51,87]. The safety, efficacy and tolerability of Perampanel as adjunctive therapy in patients with refractory partial-onset seizures have been demonstrated in many Phase III, randomized, double blind, placebo-controlled trials (Table 1) and several extension studies [21,48,59,96,97]. All these studies build a strong evidence to support the efficacy of Perampanel, as adjunctive therapy in treatment of refractory partial-onset seizures.

A Phase III study showed that administration of Perampanel continued the recovery of seizure score and seizure frequency in terms of safety and efficacy in adolescent patients with drug resistant partial seizures [88]. Another Phase III study showed the positive outcome of adjunctive Perampanel in primary generalized tonic clonic seizures (PGTC) in adolescent patients as it significantly attenuated the frequency of seizures in patients with drug resistant PGTC seizures [49]. Recently, 2 Phase 4 trial for the rational polytherapy using Perampanel dual therapy anticonvulsant combination treatments of adults with refractory focal epilepsy and the evaluation of the efficacy of Perampanel added to monotherapy for partial onset seizures with or without secondarily generalized seizures and has been started in 2015/2016 and expected time for completion is 2018 [78,104].

3.18. TRI476

Oxcarbazepine (TRI476) is a second generation AED approved as initial or add-on therapy for partial epilepsy patients. In a randomized controlled trial, adjunctive once-daily SPN-804 (extended release formulation of Oxcarbazepine) has been shown to improve seizure control in patients with refractory partial-onset seizures [47]. Currently, the long term safety and efficacy of TRI476 are being evaluated in a multicentric Phase III trial in children with inadequately controlled partial onset seizures, to completed in May 2016 [63].

4. Discussion & conclusion

In the past few decades, several new antiepileptic drugs have been developed for the treatment of seizures and epilepsy but most of the available antiepileptic drugs (AEDs) are not showing any efficacy in patients with refractory epilepsy. Thus, there is a need for discovery and

development of some novel antiepileptic agents with more efficacy and safety in treating the refractory seizures. Currently, the research should be focused on the newer strategies to develop the novel compounds by targeting the mechanisms involved in epileptogenesis and pharmacoresistance. In this review, we discussed about the current scenario in the development of investigational drugs possessing antiepileptic potential. Most of the researchers and pharmaceutical industries have adopted three main approaches for developing new antiepileptic drugs including, i) structural modification of existing drugs, ii) compounds targeting the novel mechanisms, and iii) non-mechanism based screening of drug compounds in conventional and newer animal models of epilepsy.

Seletracetam and brivaracetam are developed from structural modification of already approved antiepileptic drug, levetiracetam. These both act by the similar mechanism, binding with synaptic vesicle 2 protein (SV2A). Seletracetam possessed the greater affinity towards SV2a as compared to levetiracetam. Both analogs (seletracetam & brivaracetam) are currently under the various stages of clinical development [25,56,75]. Another drug, bumetanide, has a potential use in treatment of patients with temporal lobe epilepsy (TLE) having defective chloride homeostasis because of its novel mechanism of action by inhibiting Na-K-Cl co-transporter (NKCC). In a clinical study, bumetanide has shown a significant efficacy by reducing the number of seizures and epileptiform discharges in patients with TLE [42]. Selurampanel, a competitive AMPA antagonist, has gained a considerable interest of pharmaceutical industry. It has shown a potential anticonvulsant activity in several rodent models of epilepsy. Selurampanel is currently being in Phase-II of clinical development for treatment of patients with partial epilepsy. Another AMPA receptor antagonist, Perampanel, has shown adequate evidence supporting its efficacy and tolerability as adjunctive therapy in partial onset refractory seizures and in primary generalized tonic clonic seizures [49,59,96]. Similarly, Ganaxolone (GABA modulator), Naluzotam (serotonergic drug) and Cannabidiol are in pipeline of clinical development for treatment of focal seizures and related syndromes. Carisbamate (RWJ-333369), a novel neuromodulator, is currently under the clinical development for treatment of epilepsy. Its efficacy has been confirmed in a Phase II clinical study and currently, only one Phase III clinical trial showed its antiepileptic effect. A produg of oxcarbazepine, eslicarbazepine, has been approved as adjunctive treatment for refractory partial onset seizures [43]. In an ESLIBASE retrospective study, eslicarbazepine was found to be well tolerated and effective in patients with focal seizures [105]. Retigabine has shown the anticonvulsant activity in animal model of epilepsy and acts by a distinct mechanism through potassium channels and GABA receptor modulation. It has shown efficacy and tolerability in patients with refractory epilepsy. Everolimus (mTOR complex I inhibitor) has also demonstrated a significant benefits in TSC refractory epilepsy patients. It is currently being studied to confirm its efficacy and tolerability in large number of patients.

There is a significant need for the development of newer antiepileptic drugs targeting the novel mechanism, for treatment of refractory seizures and intractable epilepsy and thus, help the patients to lead a normal life. Drugs targeting epileptogenesis (development of seizures) are urgently needed. The advances in preclinical and clinical drug development provide a hope towards the discovery and development of new molecular entities with more efficacious and well tolerated antiepileptic potential.

About 70% patients with epilepsy can be treated with drugs which make epilepsy the best treatable neurological condition. No doubt, new AEDs are available in market but still 30% of patients resistant to available therapy. In such cases, patients are subjected to combination therapy/polytherapy which in turn results in severe side effects and complex pharmacokinetic drug interactions. Besides the presence of old as well as new AEDs, still there is a need of new drugs or modified version of old drugs to make patients, free of seizures. A better knowledge of pathophysiology of epilepsy will help in understanding and development of new drug targets and this in turn can be aimed to design and develop new therapeutics entities/options in order to prevent or suppress seizures refractory to conventional drug therapy. Patients with epilepsy become dependent, sympathetic and miserable. It affects their quality and comfort of life. The side effects or adverse effects associated with AED therapy further rise to a negative impact on the life of epileptic patients. The development of safe and effective treatments for epilepsy is a major challenge to experimental and clinical neuroscience. From the various systematic reviews and analyses of data from experimental studies, it has been concluded that the experimental data which are valid and precise should be considered to translate to clinical trial.

Available animal models are not only contributing to preclinical screening of new antiepileptic drugs but also providing a useful platform for improving our understanding about the process of epileptogenesis. There should be an optimistic approach to translate the success of preclinical testing to clinical practice. Preclinical research should be refined so that animal models mimic the human condition perfectly and convert it into positive clinical output. In recent years there is a tremendous achievement in AED development but still epilepsy remains a major therapeutic challenge and effective, better tolerated, improving quality of life, the trio which are the ideal characteristics of AED still far away. The challenge for developing side effect free AED is by being more specific to the targets and by exploring the underlying mechanism of pathophysiology in depth. This will lead us novel and ideal compounds from bedside to bench translation. For the past 15 years, new generation of AED has been coming to the market. Many of them were the structural modification of old existing AED holding promises of lesser side effects and improved stability. Some of them used either as alone or in combination therapy. But their use is limited in combination therapy due to drug–drug interactions and also restricted to specific conditions of epilepsy. There are a number of novel antiepileptic compounds which are under various stages of drug development. These drugs are expected to provide better treatment options for epilepsy in terms of improved pharmacokinetics, safety and efficacy. So, the major concern is to reduce the economic as well as social burden on patients. There is an urgent need to improve animal models and explore new targets with better knowledge in order to develop the novel drugs for treatment of patients with refractory epilepsy.

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