Antiepileptic drugs: progress and development

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Epilepsy remains one of the most challenging diseases worldwide. According to the WHO, ~50 million people around the world experience epilepsy with all its implications on the patient's overall quality of life and social life as well as social stigma. The causes of epilepsy are mostly unknown. Epilepsy treatment is considered as a huge economic burden on the patient and health care systems. This review aimed to shed light on the different types of epilepsy, the different mechanisms of action of the most novel antiepileptic drugs in the market, as well as the current antiepileptic drugs under investigation and undergoing clinical trials.

Keywords:
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Introduction

Epilepsy is a chronic brain disorder characterized by spontaneous (unprovoked) recurrent epileptic seizures that could be focal or generalized [1,2]. Epilepsy is a life-shortening condition accompanied with considerable comorbidities, including increased mortality, anxiety, and depression [3]. It affects ~1–2% of the population worldwide [4,5]. Epilepsy exerts a huge economic burden on both developed and developing countries [6,7].

Most of the causes of epilepsy are idiopathic. However, different potential etiologies have been proposed for epilepsy including brain tumor, genetic predisposition, central nervous system infection, stroke, head trauma, drug and alcohol withdrawal, and metabolic abnormalities [8–10]. Seizures occur owing to electrical disturbances of cortical neurons, leading to an immediate imbalance between inhibitory and excitatory activities, resulting in a net excitation [11].

Prevalence in Egypt

In Egypt, there are no available data for the overall prevalence and incidence of epilepsy. However, few epidemiological studies have been reported from Al-Quseir, Al Kharga, and El-Minia cities. Interestingly, epilepsy epidemiological studies from Al-Quseir City-Red Sea Governorate and Al Kharga District-New Valley Governorate revealed that the lifetime prevalence rate is 5.5/1000 and 6.76/1000, respectively, with the highest peak during early childhood. The annual incidence rate is 48/100 000 and 43.14/100 000, respectively, showing high incidence in early infancy and elderly life. The epilepsy treatment gap was 83.8 and 61.5%, respectively [12,13].

Another study evaluated the prevalence of epilepsy in primary school children in El-Minia City, Egypt. The lifetime prevalence rate was 7.2/1000 in conventional schools and 133.3/1000 in mentally subnormal children in Elfikria School for subnormal males. The male to female ratio was 2 : 1. The frequency of generalized seizures was more than partial. Moreover, 62.2% of the school children were receiving treatment. The prevalence rate was significantly higher between lower socioeconomic classes. The most common risk factors for the development of epilepsy in those children were perinatal, neonatal insult, febrile convulsions, parent of consanguineous marriage, and family history of epilepsy [14].

Egyptian contribution to epilepsy

Ancient Egyptians were the first to describe neuroscience in terms of brain, epilepsy, migraine, tetanus, strokes, and head injuries [15]. Discovered papyrus and artwork displays neurological patients. Medical ancient Egyptian texts dating back to 1700 BC were the first to describe focal seizures. A condition called 'nesejet' was mentioned in an original papyrus describing five patients experiencing involuntary convulsions of the body [16]. According to Herodotus, in ancient Egyptian civilization, there

were doctors specialized in head diseases and could therefore be considered the profounder of all neurologists [15].

In this era, there is an enormous research work for Egyptian researchers in scientific databases in the field of epilepsy. Among these, the following articles were selected from the most recently published.

Discovering novel anticonvulsant candidates from synthetic origin: a series of (1-(benzyl (aryl) amino) cyclohexyl) methyl esters (14 compounds) were synthesized and evaluated for their anticonvulsant effect. Butyl-derivative and 4-chlorophenyl-derivatives showed pronounced anticonvulsant effect without neurotoxicity in minimal motor impairment test and hepatotoxicity in the serum enzyme activity assay. The results of sc-pentylenetetrazole (PTZ) activity of the screened compounds **7a-n** were consistent with the molecular modeling study [17].

The synthesis of novel naphthalen-2-yl acetate and 1,6-dithia-4,9-diazaspiro [4.4]nonane-3,8-dione derivatives was studied. The diazaspiro nonane and 1-(2-naphthyl)-2-bromoethanone demonstrated a significantly high delay in the onset of convulsion, as well as prolongation of survival time compared with the reference drug. The molecular modeling study of the synthesized compounds displayed modulation of benzodiazepine allosteric site in γ-aminobutyric acid (GABA)-A receptors [18].

The medicinal plant, *Phragmanthera austroarabica*, at doses of 400 and 800 mg/kg significantly demonstrated anticonvulsant and neuroprotective activities in PTZ-induced kindling model in mice [19].

Moreover, electroconvulsive therapy (ECT) was studied by Ragab and Elaghoury in 2017, who evaluated the safety and efficacy of the ECT in an adolescent with intractable epilepsy, and psychiatric morbidity. ECT was found to be safe, rise the seizure threshold, reduce seizure frequency, and improve psychiatric morbidity usually accompanied with patients with epilepsy. These data pointed out the importance of ECT as a practical therapeutic option for intractable epilepsy [20].

Recently, Tawfik *et al.* [21] demonstrated the neuroprotective mechanisms of intraperitoneal administration of sildenafil and selenium in PTZ model through amelioration of the nitric oxide/oxidative stress pathway as well as modulation of angiogenesis.

Types of seizures in epilepsy

Epilepsy is classified into different types, including generalized and focal epileptic seizures, and epileptic spasms [22,23].

Generalized epileptic seizures

Generalized seizures account for ~40% of all seizures [24]. Their onset is characterized by bilateral symmetric electrical activity recorded in both hemispheres [8]. This results in abnormal motor activity and/or loss of consciousness.

Generalized seizures include the following main subtypes.

Tonic

A continuous increase in the muscle contraction that lasts from few seconds to minutes and may comprise vibratory symptoms.

Clonic

Regularly repetitive contraction, which encompasses the same muscle groups, occurs at a frequency of two to three cycles/s and could be prolonged.

Tonic–clonic

The seizures involve both tonic and clonic components.

Myoclonic

Involuntary, sudden, brief (<100 ms), single or multiple, irregular contraction(s) of muscles or muscle groups resulting in quick jerks of the body or a single limb.

Absence

Transient attacks of unconsciousness that occurs mainly in children.

Atonic

A sudden loss or decrease of muscle tone without preceded myoclonic or tonic component lasting 1- more than or equal to 1 s. Head, jaw, trunk, or limb musculature is involved in the event.

Recently, some new types of seizures were reported such as follows.

Myoclonic tonic

Jerk movements that are directly followed by few seconds of tonic stiffening of the limbs.

Myoclonic absence

Seizures are characterized by sudden onset of staring and unresponsiveness (absence seizure) followed by

myoclonic jerks of the arms and/or legs that usually last 10–60 s.

Eyelid myoclonia

Noticeable jerking of the eyelids and usually with jerky upward deviation of the eyeballs and the head. It may be accompanied with absence. The seizures usually last from 3 to 6 s and mainly occur after eye closure many times *per* day.

Focal epileptic seizures

Focal (partial) seizures account for ~60% of all seizures [24]. They originate focally within networks in one cerebral hemisphere. The seizures may be individually localized or more widely distributed.

Focal seizures include the following main subtypes

Simple partial

It is characterized by no impairment of awareness or consciousness. Seizures are either with observable autonomic or motor components. It also involves only subjective sensory, visual, or psychic phenomena, which correspond to the concept of an aura.

Complex partial

The seizures are characterized by impairment of consciousness or awareness, responsiveness, and cognition. It involves temporal or psychomotor seizures.

Partial seizure evolving to generalized seizure

The partial (focal) seizure evolves to a bilateral, convulsive seizure, which includes tonic or clonic, or tonic and clonic components.

Epileptic spasms

Although these seizures are frequently bilaterally symmetric, they may often have focal brain pathology. It is not clear whether they are of focal or generalized onset or both, as it depends on the individual condition. This seizure type occurs at old ages, either as a continuation of spasms beginning in infancy or new ones [25]. Epileptic spasms may include rhythmic eye movements, chewing and swimming movements, sudden extension of both arms, and flexion of the neck.

Antiepileptic drug selection

Selection of the ideal antiepileptic drug (AED) for every single patient can be an overwhelming process. Every AED has distinctive characteristics, which include activity, cost, pharmacokinetics, and pharmacodynamics profiles. The choice of AED treatment should not be restricted to the classification of epilepsy type, mechanism of action, drug interactions, and adverse effects. Special concern should be given to older adults, women, patients with other medical comorbidities, and to newly diagnosed patients [26–28]. Thus, the selection of AED depends on a combination of these variables and patient characteristics. It is important to realize that treatment initiation will be followed with a rational sequence of issues that should be considered to optimize drug choices [29].

Mechanisms of action of antiepileptic drugs

AEDs in first-generation, second-generation, third-generation and clinical development trials are classified according to their mechanism(s) of action.

Potentiation of inhibition by GABA

GABA is the main inhibitory neurotransmitter in the brain [30]. The GABA system can be enhanced by the following:

(1) Binding directly to GABA-A receptors: GABA binds to two types of receptors: GABA-A and GABA-B. The GABA-A receptors are coupled to chloride channels, so upon binding of GABA to GABA-A receptor, the negativity of the cell increases owing to the influx of chloride (Cl^- ion). This results in more negative resting membrane potential and thus decreases the excitability of the postsynaptic membrane [31]. GABA-B receptors are coupled to presynaptic potassium channels which may indirectly inhibit the neurotransmitters release.
(2) Blocking presynaptic GABA re-uptake: GABA re-uptake inhibitors block the GABA transporter 1, resulting in inhibition of GABA re-uptake at the synapse [32].
(3) Inhibiting the metabolism of GABA: GABA metabolism is mediated by GABA transaminase enzyme; therefore, its inhibition leads to accumulation of GABA at the postsynaptic receptors [33,34].
(4) Increasing the synthesis of GABA: GABA is produced by decarboxylation of glutamate which is mediated by glutamic acid decarboxylase enzyme. Modulation of this enzyme using certain AEDs leads to enhanced production of GABA and downregulation of glutamate [35,36].

First-generation AEDs: Bromides (in 1857) were used for generalized tonic–clonic, myoclonic seizures, and focal seizures. It is not widely used anymore. Currently, it is used as adjunctive only, as it acts as a sedative. Phenobarbital (in 1912) is effective against focal seizures and generalized tonic–clonic seizures

(GTCSs) but is not effective against generalized absence seizures. Primidone (in 1954) is converted in the liver to phenobarbital and active metabolite, phenylethylmalonamide. Primidone is effective against focal seizures and GTCSs [2,37].

Second-generation AEDs: Diazepam (in 1963), clonazepam (in 1968), and clobazam (in 1975) are used as an adjunctive therapy in generalized seizure types [37].

Third-generation AEDs: Progabide (in 1985) is used in partial, generalized, myoclonic seizures, and Lennox–Gastaut syndrome (childhood epilepsy characterized by the occurrence of frequent seizures of multiple types accompanied by an abnormal electroencephalograph pattern, and intellectual impairment of variable intensity) [38,39]. Vigabatrin (in 1989), an irreversible inhibitor of GABA transaminase, is a narrow-spectrum drug effective against focal seizures. Tiagabine (in 1996) Gabitril is a GABA re-uptake inhibitor with a narrow spectrum of efficacy against focal seizures only [40].

AEDs in clinical development phase: Muscimol is a selective potent agonist of the GABA-A receptor [41]. It binds to the GABA binding site on the GABA-A receptor complex on the contrary to other GABAergic drugs as benzodiazepines and barbiturates which bind to separate regulatory sites [42]. In the brain, the GABA-A receptors are broadly distributed.

Therefore, muscimol has the ability to alter neuronal activity in multiple regions in the brain including cerebral cortex, cerebellum, and hippocampus. Muscimol was originally isolated from the poisonous fungus *Amanita muscaria*. It is the major active principle, as psychoactive alkaloid, in this fungus and is present in many mushrooms of the genus *Amanita* [43]. A clinical trial was carried out to investigate the safety and effectiveness of muscimol infusion into the brain for controlling seizures in patients with intractable epilepsy (ClinicalTrials.gov Identifier: NCT00005925, Last update: July 2018).

Voltage-gated sodium channel blockade

The depolarization phase of the neuronal action potential occurs by allowing sodium influx through Na^+ channels. This results in an active phase that is followed by an inactive refractory period. Certain AEDs stabilize this inactive state and block the depolarization of the nerve terminal, thus preventing the high-frequency neuronal firing that leads to seizures [36,44].

First-generation AEDs: Phenytoin (in 1938) is effective against focal seizures and GTCSs. Phenytoin is not effective against generalized myoclonic or generalized absence seizures and may even exacerbate these seizures; hence, it is not a drug of choice in idiopathic generalized epilepsy.

Second-generation AEDs: Carbamazepine (in 1964) is effective against focal seizures and GTCSs.

Third-generation AEDs: Lamotrigine (in 1990) is a broad-spectrum AED, although its Food and Drug Administration (FDA) indications are limited to focal seizures, GTCSs, and Lennox–Gastaut syndrome. Oxcarbazepine (in 1990) is effective against focal seizures [37]. Currently, a phase III study is carried out to examine the long-term safety data of oxcarbazepine in children with inadequately controlled focal seizures (ClinicalTrials.gov Identifier: NCT01051193, Last update: June 2018). Rufinamide (in 2004) is a broad-spectrum AED, but its efficacy against focal seizures was not sufficient for FDA indication. Lacosamide (in 2008) blocks sodium channels, enhancing slow inactivation, unlike most classic sodium channel blockers, which enhance fast Na^+ channel inactivation. Lacosamide appears to be a narrow-spectrum AED against focal seizures [45].

Eslicarbazepine acetate (in 2009) Zebinix by Eisai Co. Ltd. (in 2009 approved in European union) and Aptiom by Sunovion Pharmaceuticals Inc. (in 2013 approved by FDA): Eslicarbazepine acetate is effective against focal seizures and is used as adjunctive therapy for partial seizures alone or those evolving to secondary generalization [46]. Eslicarbazepine acts by blocking sodium channels and stabilizing the inactive state of the voltage-gated Na^+ channel. A phase III clinical trial showed its effectiveness for long-term monotherapy of partial-onset seizures (ClinicalTrials.gov Identifier: NCT01162460, Last update: September 2016). A retrospective study showed that it is effective and tolerated in patients with focal seizures [47]. Another phase III trial is being carried out to study its use as adjunct therapy for refractory partial seizures (ClinicalTrials.gov Identifier: NCT00988429, Last update: February, 2017).

Calcium channel blockade

(1) T-type calcium channel blockade
In the thalamic neurons, T-type calcium channels play an important role in the 'spike and wave' discharges of absence seizures. The influx of calcium in the membrane resting state results in

partial depolarization of the membrane, enabling the development of an action potential after rapid depolarization of the cell. The inhibition of T-type calcium channels by AEDs leads to reduction of low-threshold T-type calcium currents and is effective against absence seizures [30,48].
First-generation AEDs: Trimethadione (in 1946) is used for absence seizures, but not in wide use anymore owing to teratogenicity [49]. Ethosuximide (in 1958) is used for absence seizures [50].

(2) Calcium channel (α2δ subunit) blockade
The AEDs of this type bind to the α2δ subunit of voltage-gated calcium channels resulting in reduction of the influx of calcium and the associated neurotransmitters released under hyperexcitable conditions [9].
Third-generation AEDs: Gabapentin and pregabalin (in 2004) are used against focal seizures but may exacerbate myoclonic and absence seizures [51,52].

Action on α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid and N-methyl-D-aspartate

α-Amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) and N-methyl-D-aspartate (NMDA) are glutamate receptor sites, which bind the excitatory neurotransmitter, glutamate, resulting in the activation of Ca^{2+} and Na^{+} ions influx and K^{+} ions efflux leading to excitation. Thus, AEDs acting as glutamate antagonists modify these receptors and inhibit the excitatory effect [53,54].

Third-generation AEDs: Perampanel (in 2012) as Fycompa developed by Eisai Inc. is highly selective noncompetitive AMPA glutamate receptor antagonist acting on postsynaptic neurons resulting in inhibition of the excitatory postsynaptic function [55]. It is indicated as adjunctive treatment in refractory partial-onset seizures and primary GTCSs [56]. A recent retrospective study by Morano *et al.* [57], demonstrated that patients' response to perampanel treatment in secondarily GTCSs is better than primary GTCSs and focal seizures.

Perampanel is effective for focal seizures with or without secondarily generalization and tonic–clonic generalized seizures [56,58]. Perampanel demonstrated anticonvulsant activity in electroshock and chemically induced seizures in rodents in preclinical animal models [59].

Selurampanel is developed by Novartis Pharmaceuticals Corporation as an oral competitive antagonist of the AMPA/kainate receptors with good oral bioavailability and blood–brain barrier (BBB) penetration [60]. Currently, selurampanel is being investigated in development clinical trials by Novartis Pharmaceuticals Corporation for the treatment of epilepsy.

Two phase II studies are carried out to investigate its use as adjunctive treatment in patients with partial epilepsy (ClinicalTrials.gov Identifier: NCT01147003, Last updated: March 2013, no study results posted) as well as its effect in patients with photosensitive epilepsy (ClinicalTrials.gov Identifier: NCT00784212, Last updated: September 2016, no study results posted). A proof-of-concept of this phase II study has been published for demonstrating the dose-dependent positive effect of selurampanel on the photoparoxysmal response in patients with photosensitive epilepsy. This result supports further investigation of AMPA receptor antagonists in phase III trials [61].

Antiepileptic drugs with multiple mechanisms of action

(1) GABA potentiation, NMDA receptor antagonist, sodium channel blockade, and calcium channel blockade.
Second-generation AEDs: Valproate (in 1967) has a wide spectrum of efficacy against all focal and generalized seizures, including absence and myoclonic seizures [37].
Third-generation AEDs: Felbamate (in 1993) is a broad-spectrum agent effective against focal seizures as well as generalized seizures in the setting of Lennox–Gastaut syndrome (a severe epileptic encephalopathy that affects children) [62].

(2) GABA potentiation, AMPA/kainate receptors antagonist, sodium channel blockade, and calcium channel blockade.
Third-generation AEDs: Topiramate (in 1995) is a broad-spectrum AED effective against focal and GTCSs [62,63].

(3) GABA potentiation and sodium channel blockade.
Third-generation AED: Stiripentol (in 2002) is used for Dravet syndrome (severe myoclonic epilepsy in infancy) [64].

(4) T-type calcium channel blockade, sodium channel blockade, and inhibition of glutamate release.
Third-generation AED: Zonisamide (in 2000) is considered a broad-spectrum AED for focal and generalized seizures [2].

Synaptic vesicle protein 2A modulation

Synaptic vesicle protein 2A (SV2A) is a synaptic vesicle protein that plays an important role in vesicle

exocytosis and ejection of stored neurotransmitters [65,66]. AED binds to the synaptic protein SV2A, resulting in nonspecific decrease in neurotransmitter release [67].

Third-generation AEDs: Levetiracetam (in 2000) is a broad-spectrum drug effective against focal seizures, GTCSs, and generalized myoclonic seizures. It is the first-line AED for intravenous use with no recorded clinical hepatotoxicity [2].

Newly marketed drugs: Brivaracetam (Briviact) was approved by FDA on February 2016. Its mechanism of action involves binding to SV2A and blocking sodium channel. A total of 17 studies are in phase III to assess the efficacy and safety of brivaracetam in patients, as adjunctive intravenous or bolos antiepileptic therapy, and in patients with partial-onset seizures (Last updates for the clinical trials in the duration between May 15, 2015 and March 28, 2017).

AEDs in clinical development phase: Seletracetam (phase II) possesses high binding affinity to SV2A [68] and inhibits N-type calcium channels and preventing influx of Ca^{2+} during high-voltage activation [69]. Two studies have been completed in phase II to evaluate seletracetam in adult patients with partial-onset seizures (ClinicalTrials.gov Identifier: NCT00152451, Last updated: February 2017) and to study the efficacy and safety of seletracetam as add-on in patients with focal epilepsy and currently taking levetiracetam (ClinicalTrials.gov Identifier: NCT00152503, Last updated: September 2008).

Potassium channel activation

The efflux of potassium ion is partially responsible for the refractory period after an action potential. Potassium channel (KCNQ2-5) opener AED modifies this outward potassium current to flow faster. This results in augmentation of the refractory period leading to slowing of the repetitive firing of neurons [70].

Third-generation AEDs: Retigabine (Ezogabine) (in 2011) Trobalt, is a novel AED with a unique mechanism of action. Retigabine is a narrow-spectrum AED effective only against focal seizures [65,70]. It was declared that retigabine production will be discontinued on June 2017, as safety issues were announced in 2013 by the manufacturer GlaxoSmithKline around the drug, as it may cause blue discoloration of the skin and abnormalities of the eye characterized by pigmentation in the retina.

Mammalian target of rapamycin inhibition

Everolimus, Afinitor, was developed by Novartis Pharmaceuticals Corporation [71]. The drug everolimus is approved by the FDA to treat specific types of breast, pancreatic, and kidney cancer. Everolimus is used in patients with tuberous sclerosis complex (TSC), where epilepsy is a major disorder of this disease condition. Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR) with beneficial effects in several aspects of TSC [72]. The mTOR pathway has been examined in pilocarpine-induced status epilepticus in rat to develop medial temporal lobe epilepsy and eventually spontaneous seizures [73].

A phase II clinical trial is currently investigating the role of everolimus on brain mTOR signaling activity in patients having TSC and focal cortical dysplasia who are resistant to epilepsy treatment and will be undergoing brain surgery. As patients with focal cortical dysplasia may also have excess mTOR signaling brain activity, everolimus may also reduce seizure activity in these patients (ClinicalTrials.gov Identifier: NCT02451696, Last update: July 2018). A phase III clinical trial was carried out to evaluate the efficacy and safety of two different ranges of everolimus administered as adjunctive therapy in patients having both TSC and refractory partial-onset seizures (ClinicalTrials.gov Identifier: NCT01713946, Last update: February 2018).

Drugs acting through other mechanisms of action

Bumetanide (Bumex or Burinex) is used in market as a loop diuretic. Bumetanide is an inhibitor of Na–K–Cl cotransporter (NKCC). There are two isoforms of NKCC expressed in the body. The ubiquitous NKCC1 is also expressed in central and peripheral neurons as well as glial cells [74] whereas NKCC2 is selectively expressed in the kidney [75]. In the brain, bumetanide blocks the NKCC1 and thus decreases internal Cl^- ion concentration in the neurons [76]. This change in concentration potentiates the action of GABA leading to more hyperpolarization, which is beneficial for treatment of neonatal seizures, which are not usually responsive to barbiturates as traditional GABA-targeted treatment [77]. In addition, bumetanide treatment declined PTZ-induced seizure susceptibility and cognitive recovery in PTZ-induced rats suffering from hypoxia-ischemia injury during neonatal period. These results were attributed to bumetanide ability to restoring the ectopic newborn neurons in dentate gyrus and cognitive function [78].

Currently, phase I pilot study of bumetanide is being carried out to investigate its pharmacokinetic profile and safety in newborns with refractory seizures (ClinicalTrials.gov Identifier: NCT00830531, Last updated: April 2018).

Cenobamate (YKP3089) was developed by SK-Biopharmaceuticals (in 2015). It possess a broad-spectrum anticonvulsant efficacy in different rodent models of epilepsy [79]. Cenobamate mechanism of action is currently under investigation. The proposed mechanism of action is selective sodium channel blocker, and it facilitates presynaptic GABA release [80]. The compound is being developed as an oral therapy for epilepsy, bipolar disorders, and neuropathic pain [81].

Currently, a phase III trial is ongoing to study safety and pharmacokinetics of cenobamate as adjunctive therapy in patients with partial seizures (ClinicalTrials.gov Identifier: NCT02535091, Last updated: June 2017). Cenobamate is well tolerated and has been shown to be effective in patients with photosensitive epilepsy in a phase II trial (ClinicalTrials.gov Identifier: NCT00616148, Last updated: January 2014). A phase II trial of cenobamate is being conducted as adjunctive therapy in patients with partial-onset seizures (ClinicalTrials.gov Identifier: NCT01866111, Last updated: April 2018). Moreover, a phase II development is underway to investigate its potential therapeutic use in neuropathic pain and bipolar disorders http://adisinsight.springer.com/drugs/800023388.

Naluzotan (PRX-0023) is a selective serotonin 5-HT1A receptor agonist [82]. Activation of 5-HT1A inhibits seizures through hyperpolarization of glutamatergic neurons. A previous study suggested the possible lower serotonin activity in brain areas, where seizures are initiated [83]. A phase II clinical trial is investigating the effects of naluzotan on seizure frequency that starts from only one part of the brain (ClinicalTrials.gov Identifier: NCT01281956, Last updated: July 2018).

Verapamil is a P-glycoprotein (Pgp) inhibitor and calcium channel blocker. Pgp is a multidrug transporter protein in the BBB which limits the uptake of substrate drugs into the brain and thus restricts the access of some AEDs to their site of action [84,85]. It is also responsible for elimination of drugs [86]. Verapamil mechanism of action is mainly attributed to the blocking of the Pgp-modulated efflux of AEDs in the brain, thereby raising the intracellular concentration of AEDs [87]. Verapamil may lower the seizure burden through inhibiting the metabolism of carbamazepine by CYP450 enzyme. Therefore, concurrent administration of the two drugs leads to an elevation in carbamazepine serum level and potentially increases its efficacy and/or toxicity [88].

A pilot study demonstrated that the use of verapamil as an adjunctive therapy in patients with refractory temporal lobe epilepsy resulted in significant achievement in the seizure control [89]. Administration of verapamil demonstrated promising results in patients with drug-resistant epilepsy, such as Lennox–Gastaut syndrome, Dravet syndrome, focal epilepsies, or status epilepticus [85]. A phase II clinical trial was carried out to assess verapamil as an adjunctive therapy for seizures in children and young adults with Dravet syndrome (ClinicalTrials.gov Identifier: NCT01607073, Last updated: March 2015). Verapamil may offer pharmacoresistant patients hope for improved seizure control, owing to its potential Pgp inhibitory effects.

Carisbamate (RWJ-333369) (proposed trade name is Comfyde) was initially developed by SK-Biopharmaceuticals and Johnson & Johnson. It is not yet given FDA marketing approval. It is considered as a neuromodulator drug and a broad-spectrum anticonvulsant whose mechanism of action has not been fully investigated [90]. The drug displayed neuroprotective and antiepileptogenic effect in lithium-pilocarpine status epilepticus rat model [91]. According to the search in clinicaltrails.gov, several clinical trials were completed investigating the safety and either efficacy or tolerability in patients with epilepsy or partial-onset seizures alone or as an adjunctive therapy.

Cannabidiol: some pilot studies have demonstrated that natural or synthetic cannabidiol products proved beneficial for refractory epilepsy. However, more rigorous clinical trials are needed to confirm their efficiency. Cannabidiol has been shown to be effective in maximal electroshock model of epilepsy [92] and PTZ [93]. Although it possesses potential efficacy in epilepsy, the precise mechanism of action is not entirely clear. This could be attributed to the diverse pharmacological effects of cannabidiol, which involve simultaneous modulation and/or inhibition of neuronal hyperexcitability [94,95]. Multiple presumed mechanisms of action for cannabidiol have been studied including its effect on NMDA and serotoninergic (5HT1α) receptors, regulation of Ca^{2+}

mobilization, or potentiation of GABA receptors inhibition [96]. In January 2018, an open-label single-group assignment trial was started to evaluate the safety of fenfluramine hydrochloride, a serotonin releasing agent formerly used as appetite suppressant, in combination with cannabidiol, as an adjunctive therapy in children and young adults with Dravet syndrome or Lennox–Gastaut syndrome (ClinicalTrials.gov Identifier: NCT03467113).

Adverse effects of certain antiepileptic drugs

The common adverse effects of AEDs are drowsiness, dizziness, and mental slowing, in addition to changes in weight, movement, and behavioral disorders, metabolic acidosis, enzyme induction, visual adverse effects, hypohydrosis and heat intolerance, hepatotoxicity, movement and behavioral disorders, dermatological adverse reactions, nephrotoxicity, and colitis [97]. Moreover, it is remarkably noticed that patients who respond efficiently to the AEDs treatment are subjected to systemically high concentrations of the medications to accomplish therapeutically powerful levels at the site of activity in the central nervous system. This leads to undesired adverse effects that severely affect their adherence to the treatment and their quality of life [98].

Withdrawing antiepileptic medication

Certain factors such as adolescent-onset epilepsy, abnormal electroencephalograph, partial seizures, or abnormal neurologic examination at the time of withdrawal increase the risk of seizure recurrence in patients withdrawing off AEDs. The recurrence of seizure after withdrawal of AED could be more tolerated in young children. On the contrary, the effect on adults would be of significant negative psychosocial and financial consequences. Interestingly, successful withdrawal off AED treatment imparts the important benefits of avoiding the adverse effect of long-term treatment and dose-related adverse effects [99].

Development of nanoformulations of antiepileptic drugs

Nanoformulation is one of the most recent approaches in the development of AEDs. This novel promising strategy aims at improving the pharmacokinetic properties via enhancing the therapeutic concentrations of AEDs in the central nervous system. Regular routes of administration of AEDs involve mainly the oral and intravenous routes. High drug doses are usually taken via these routes to maintain high drug concentration in the blood stream to be capable to reach the brain via crossing the BBB at the therapeutic needed dose [100].

In pharmaceutical industry research field, enormous studies have been carried out lately encompassing drug nanoformulations. However, fewer research studies have been done on the AED nanoparticle formulation. These studies involve encapsulating AEDs into a nanosystem to overcome the obstacles faced by the high molecular weight or hydrophilicity of compounds to enhance their crossing of the BBB and hence, improving drug delivery and release [101].

Nose-to-brain delivery of AEDs: The development of intranasal AED nanoformulation is a noninvasive approach to ensure a direct drug delivery into the central nervous system via bypassing the BBB with a rapid onset of effect, minimal systemic drug losses, and excluding metabolism [102–104]. Anticonvulsant drugs such as carbamazepine [105] and lamotrigine [106] exhibited promising nose-to-brain delivery via intranasal route in experimental animals. In addition, intranasal delivery of benzodiazepines is useful in acute crisis management and seizure emergencies, as it reduces the time between drug administration and seizures cessation [107].

AED nanomedicine is a promising approach that still needs to develop in terms of preclinical and clinical trials, aiming at improving the AED therapy and accordingly the overall patient's quality of life.

Traditional herbal medicine in epilepsy

Traditional medicine and the use of medicinal plants can be traced back to ancient Egypt (4000–300 BC) [108]. It is widely used in developing countries where up to 80% of the inhabitants depend on traditional medicines for their primary health care needs [109]. Treatment of epilepsy with herbal drugs as adjuvant seems to be beneficial and is showing certain popularity owing to their fewer adverse effects [110].

In Egyptian herbal medicine, *Peganum harmala* L. and *Ruta graveolens* L. were traditionally used for the treatment of epilepsy [111]. In addition, *Anastatica hierochuntica* L. (Kaff Mariam), *Citrullus colocynthis* (L.) (Handal), *Teucrium leucocladum Boiss.* (Zaater alhr), *Datura stramonium* L. (Taturah, Nefir), *Bacopa monnieri* (Wedwad), *Globularia arabica* (Handaqoo, Zorreiqa), *Lavandula pubescens* (Attan), and *Pluchea dioscoridis* (Barnoof) were used by Bedouins in Sinai to relieve fits of epilepsy [112].

Herbs with sedating effect such as chamomile, valerian, kava, and passion flower may possibly accelerate the AED effects through potentiating their cognitive and sedative effects. On the contrary, herbs comprising stimulant active ingredients such as caffeine (cocoa, tea, coffee, kola) and ephedra alkaloids (ma huang or ephedra) as well as ginkgo biloba and ginseng formulae may lead to or aggravate seizures in patients with epilepsy [113,114]. Leaves of *Taxus wallichiana* known as Himalayan Yew are used to prepare herbal tea for epilepsy and indigestion [115].

St John's wort is contraindicated to be co-administered with AED medication as it is an inducer of CYP 2C and 3A subfamilies, thus altering the plasma level of AED administered [116]. Leaves of *Laurus nobilis* family Lauraceae are used to treat epilepsy owing to the anticonvulsant activity of the essential oils, eugenol, methyleugenol, and pinene, against maximal electroshock and PTZ-induced seizures [117]. Evening primrose oil, commonly used to treat premenstrual syndrome, was found to reduce the threshold for seizures [118]. Therefore, health care providers and patients should be aware of the herbal–herbal and herbal–drug interactions that could lead to severe adverse events [119].

Herbal formulae in Chinese traditional medicine are used as principal treatment, whereas acupuncture as supplemental treatment in epilepsy [120]. Ginseng, Gingko biloba, and St John's wort are commonly used to overcome depression, anxiety, and memory deficit symptoms, which are common comorbid conditions of epilepsy [121]. The most frequently used Chinese herbal medicines are as follows: *Valeriana officinalis*, Pepper, Rhizoma Curcumae, Uncaria, Gastrodia, and Cinnamon twig [120]. The constituents of the ancient Chinese herb, Tian ma, as well as its symbiotic fungus *Armillaria mellea* have been reported to possess antiepileptic properties in both in-vitro and in-vivo models [122].

In Ayurvedic medicine, which is commonly practiced in South Asia, particularly in India, people with epilepsy use herbal extracts prepared from *Bacopa monnieri*, *Acacia arabica*, *Acorus calamus*, *Celastrus paniculatus*, *Convulvulus pluricaulis*, *Emblica officinalis,* and *Withania somnifera* [123].

Conclusion and future prospective

Although great progresses have been achieved in AED development, ~40% of the patients are still noncompliant to treatment with conventional AEDs [124].

A substantial progress in research has to be carried out to understand the different mechanisms of action involved in the development of epilepsy, as well as the causes of drug resistance. This research would provide opportunities for the discovery and development of more effective AEDs. It is recommended that future AEDs would be developed through collaborative work between scientific research institutions, universities, and industry to identify and apply new target-driven approaches and innovative clinical trials designs.

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Conflicts of interest

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