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Insights into the novel three 'D's of epilepsy treatment: drugs, delivery systems and devices

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Here, we review three 'D's – drugs, delivery systems and devices – that can selectively target not only brain regions but also abnormal cells in the epileptic nervous system. This review also offers insights into the novel molecular targets that enabled the development of new antiepileptic drugs with improved efficacy. Nanotechnology-based delivery systems and alert, diagnostic, surgical and brain stimulation devices designed for the control and management of epilepsy are also discussed. Although the application of the three 'D's continues to be valuable, this review also considers computer-aided software systems, with special emphasis on seizure detection and management. Finally, challenges that still loiter in the field and future prospects that, once accomplished, could lead to cures for epilepsy are addressed.

Introduction

Epilepsy is operationally defined as a group of neurologic disorders characterized by recurrent episodes of convulsive seizures, sensory disturbances, abnormal behavior, loss of consciousness or all of these [1]. The word 'epilepsy' stems from the Greek *epilambanein*, meaning 'to be seized', or 'to be overwhelmed by surprise'. In ancient times, epileptic attacks were thought to be the result of invasion and possession of the body by supernatural forces, usually malign or evil influences, requiring exorcism, incantations or other religious and social approaches. Hippocrates, in the 5th century BC, first suggested that the brain was the seat of this disorder because it was also the mediator of the intellect, behavior and emotions [2]. A wide range of different seizure types and epilepsy syndromes has been identified. Infections of the central nervous system (including encephalitis, abscesses and meningitis, but excluding parasitic infestations), antenatal and perinatal risk factors, and cerebrovascular disorders were among the most frequently reported in explicating the etiology of epilepsy [3]. Although the treatment of epilepsy has made remarkable strides with the introduction of new antiepileptic drugs (AEDs), it has fallen short of expectations in terms of positive clinical outcome, with up to one-third of the patients continuing to experience seizures or unacceptable medication-related side-effects [4]. However, advances in understanding of both the causes and the mechanism of epilepsy have been

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paralleled by the rapid development of drugs, delivery systems and devices (the three 'D's). This review considers how the development of potential molecular targets might enable the development of AEDs that can selectively target not only brain regions but also abnormal cells in the epileptic nervous system. Novel delivery systems – including modified-release systems, nanoscale delivery systems, implantable devices and convection-enhanced delivery systems, which are currently under development or are in pivotal stages of clinical trials – are also discussed. This review also considers cutting-edge strategies for alert, diagnostic, surgical and brain stimulation devices designed for the control and management of epilepsy. Although the application of the three 'D's continues to be valuable, this review also considers computer-aided software systems, with special emphasis on seizure detection and management. In addition, although this article reviews various stages of development of the three 'D's, their use in epileptic patients needs clinical evidence subject to regulatory approval. Finally, we address challenges that still loiter in the field and suggest future prospects that, once accomplished, could lead to cures for epilepsy.

The first 'D': AEDs

The modern AED era – spanning a period of over 150 years from the first use of bromide in 1857–2009 – has seen the introduction into clinical practice of a diverse group of effective and safe drugs. Novel AEDs have provided considerable benefits against epilepsy of all kinds and in approximately 60–70% of epileptic patients lead to satisfactory seizure control and a favorable risk–benefit balance [5,6].

Dramatic progress in molecular fishhook techniques, in conjunction with genomics and advances in understanding the mechanisms of action of AEDs, has revolutionized the elucidation of molecular targets for AEDs. Unlike the conventional AED targets that mediate neuronal excitability mechanisms, these new targets are believed to modulate neurotransmitter release directly. The various AEDs and targets under preclinical or clinical stages and their probable mechanisms of action are described in Fig. 1. The knowledge of these new molecular targets has enabled the development of new AEDs with an improved efficacy profile and reduced side-effects (Table 1).

Ion channel modulators

Signal transduction in neurons is controlled by ion flux across the plasma membrane. Activation of ionotropic glutamate receptors (excitatory receptors) results in the influx of positive ions and, thus, depolarization. Depolarization, if sufficient, activates sodium channels (voltage-gated ion channels) at the axon and is propagated along the axon to presynaptic termini by activating more sodium channels. Furthermore, this depolarization, if adequate, activates calcium channels (mainly T-type) that stimulate neurotransmitter release [7]. The neurotransmitter activates the next neuron in the network, enabling information flow in the brain. Depolarization is competed or terminated by hyperpolarization through the influx of negative ions that results from the activation of potassium channels or gamma-amino butyric acid (GABA) receptors (inhibitory receptors) [8]. Epilepsy or seizures are the result of excessive neuronal firing (neuronal hyperexcitability) temporarily disrupting neuronal signaling. Thus, molecules that can decrease the influx of positive ions by blocking (antagonists) ionotropic glutamate receptors (excitatory receptors), sodium channels (voltage-gated ion channels) or T-type calcium channels or that can increase the influx of negative ions by opening potassium channels, by acting as agonists at GABA receptors (inhibitory receptors) or by blocking GABA re-uptake or metabolism are prime candidates for future AEDs.

The use of classical benzodiazepines and barbiturates in chronic epilepsy therapy is limited because of the development of mechanism-related side-effects, tolerance and sedation [9]. The use of valproic acid (VPA), having a wide spectrum of antiepileptic action, is also limited because of its poor pharmacokinetics and dangerous adverse effects including hepatotoxicity and teratogenecity [10].

It is not the limitations that drive scientific investigation, but the unmet clinical need accounts for intensive research and drugs with selectivity towards receptor subunits as targets are developed or are under development. The new generation benzodiazepines such as FG 8205, abecarnil, NS 2710, pagoclone and RWJ-51204 with selectivity towards receptor subunits as targets show favorable protective index and less propensity for tolerance. T2000 (1,3-dimethoxymethyl-5,5-diphenylbarbituric acid), a prodrug of 5,5-diphenylbarbituric acid, is a new generation barbiturate that does not cause sedation [11]. Preclinical data have demonstrated that new generation VPA derivatives, exemplified by isovaleramide, valrocemide and DP-VPA, are more potent and safer than VPA [12].

Recently, mutated genes in different channels – such as SCN gene for sodium channel, KCNQ gene for potassium channel, CLCN2 gene for chloride channel and CACNB4 gene for calcium channel – have been considered as novel ion channel targets [13]. The novel AEDs with selectivity towards the mutated genes (such as ICA-105665 [14] and retigabine interacting with KCNQ gene [15], J2P-4 interacting with NAV1.2A gene and eslicarbazepine interacting with site II of voltage-gated sodium channel) overcome the problems associated with traditional AEDs [16]. A novel functionalized amino acid derivative, lacosamide, is a voltage-gated sodium channel blocker with considerably improved pharmacokinetics. The results of the phase II clinical studies are promising, and phase III trials are in progress [17].

Some novel GABAergic compounds – such as clobazam and stiripentol, which increase GABA transmission through $GABA_A$ receptor; becampanel, which acts on the GABA pathway; or tonabersat, which inhibits neuronal gap junctions via the inhibition of selective connexin-mediated cell coupling – are in different phases of clinical trials [18]. On the basis of the anticonvulsant activity of naturally occurring pregnane steroids, synthetic neurosteroid ganaxolone is in the phase II clinical development stage as a first-in-class drug for the treatment of epilepsy. Ganaxolone is a powerful positive allosteric modulator of $GABA_A$ receptors, which is effective and safe for both children and adults suffering from refractory epilepsy [19]. Furthermore, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) are identified as agonists at ionotropic glutamate receptors. Thus, drugs such as talampanel and NS1209/SPD 502, which are antagonists at AMPA receptors, and huperzine A, conantokin-G and AV-101, which are antagonists at NMDA receptors, possess antiepileptic potential [20,21].

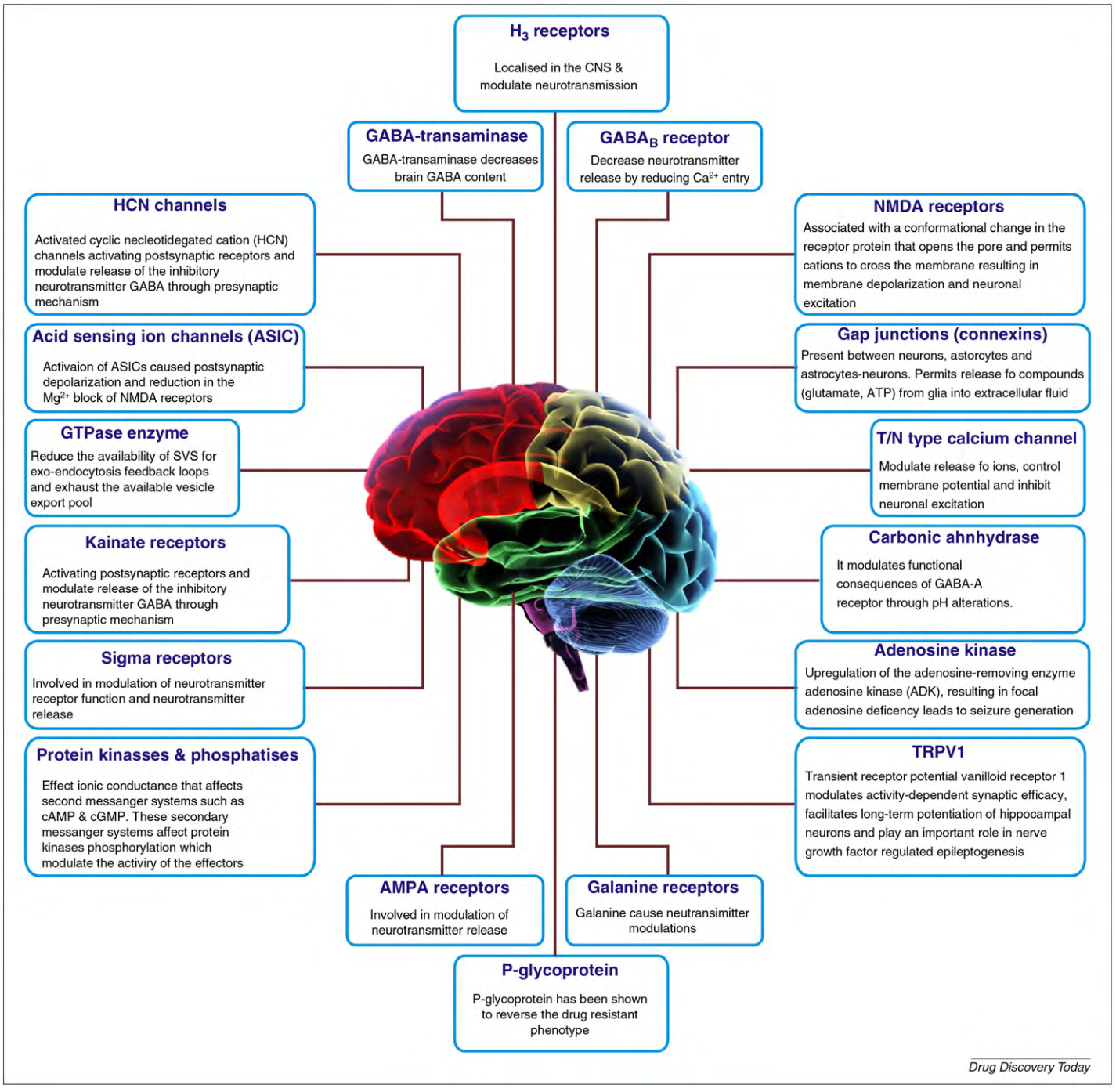

FIGURE 1

Molecular targets for the development of new antiepileptic drugs. Histamine (H_3) modulates neurotransmitter release; $GABA_B$ decreases neurotransmitter release by reducing Ca^{2+} entry; NMDA permits cations to cross the membrane, resulting in membrane depolarization and neuronal excitation; GAP junctions (connexins) permit release of glutamate and ATP from glia into extracellular fluid; T/N-Type calcium channel controls membrane potential and inhibits neuronal excitation; carbonic anhydrase modulates functional consequences of $GABA_A$ receptor through pH alteration; adenosine kinase upregulation results in focal adenosine deficiency leading to seizure generation; TRPV1 modulates activity-dependent synaptic efficacy and potentiation of hippocampal neurons; galanine causes neurotransmitter modulation; pGp reverses the drug-resistant phenotype; AMPA modulates neurotransmitter release; protein kinase and phosphotises affect protein kinase phosphorylation and modulate the activity of the effectors; SIGMA modulates neurotransmitter release; kainate modulates neurotransmitter release through presynaptic mechanism; GTPase enzyme reduces the availability of SVs for exo-endocytosis and exhausts the available vesicle export pool; acid-sensing ion channels cause postsynaptic depolarization and reduction in the Mg^{2+} block of NMDA receptors; HCN channels modulate neurotransmitter release through postsynaptic mechanism; and GABA-transaminase decreases brain GABA content.

Acid-sensing ion channel modulators

Acid-sensing ion channels (ASICs) are a family of proton-gated cation channels related to the degenerin/epithelial Na^+ channels. Six isoforms have been cloned, and these are widely expressed as homomeric or heteromeric channels in the central and peripheral nervous system. It has been suggested that protons released during high-frequency stimulation of excitatory synapses activate ASICs to cause postsynaptic depolarization. One of the consequences of

TABLE 1

Novel AEDs, their development stages and probable mechanisms of action.

Mechanism	Drug candidate	Specific site known	Development stage	Company and web address or Refs
Ion channel modulators				
Chloride channel opener	CLP635	–	Preclinical	Chlorion Inc., USA (http://www.chlorion.com)
Calcium channel blockers	C Cl's: N.T. and N./T	T-type	Preclinical	CombinatoRx Inc., USA (http://www.neuromed.com)
	JZP-4	N-, L-, P/Q-types	Phase I	Jazz Pharmaceuticals, USA (http://www.jazzpharma.com)
Sodium channel blockers	JZP-4	NAV1.2A, NAV1.3	Phase I	Jazz Pharmaceuticals, USA (http://www.jazzpharma.com)
	T-2000	–	Preclinical	Taro Pharmaceuticals, USA (http://www.tarousa.com)
	Carisbamate (RWJ-333369)	Voltage-gated Na^+ channel	Phase III	Johnson & Johnson, USA (http://www.jnjpharmarnd.com)
	Eslicarbazepine	Site-II, Na^+ channel	Phase III	BIAL-Portela & Ca, S.A., Portugal (http://www.bial.com)
	Lacosamide	Voltage-gated Na^+ channel	Phase III	Schwarz BioSciences GmbH, Germany (http://www.ucb.com)
	Safinamide	–	Phase II	Merck-Serono, France (http://www.merckserono.net)
	Rufinamide	–	Recently approved	Eisai, USA (http://www.eisai.com)
Potassium channel opener	ICA-105665	KCNQ	Phase I	Icagen, USA (http://www.icagen.com)
	Retigabine	KCNQ (Kv7)	Phase III	Valeant Pharmaceuticals International, USA (http://www.valeant.com)
GABA	Isovaleramide (NPS 1776)	GABA agonist	Preclinical	NPS Pharma, USA (http://www.npsp.com)
	Ganaxolone	$GABA_A$ agonist	Phase II	Marinus Pharmaceuticals Inc., USA (http://www.marinuspharma.com)
	Becampanel (AMP 397)	GABA pathway	Phase II	Novartis, USA (http://www.novartis.com)
	Clobazam	$GABA_A$ agonist	Phase III	Lundbeck Inc., USA (http://www.lundbeckinc.com)
	Stiripentol	$GABA_A$ agonist	Recently approved	Laboratoires Biocodex, France (http://www.biocodex.com)
	Huperzine A	NMDA antagonist	Preclinical	Anticonvulsant Screening Program, NINDS, NIH (http://www.ninds.nih.gov)
	Conantokin-G	NMDA antagonist	Preclinical	Cognetix Inc., USA (http://www.cognetix.com)
	AV-101	NMDA antagonist	Preclinical	VistaGen Therapeutics, USA (http://www.vistagen.com)
	Talampanel	AMPA antagonist	Phase II	Teva Pharma, Israel (http://www.tevapharm.com)
	NS1209/SPD 502	AMPA antagonist	Phase II	NeuroSearch Shire, UK (http://www.neurosearch.co.uk)
Acid-sensing ion channels	Amiloride	ACCN2	Preclinical	[22]
	Pyrazinoylguanidine compounds	–	Preclinical	Parion Sciences Inc., USA (http://www.parion.com)
Receptor modulators				
Synaptic vesicle protein	Seletracetam (UCB 44212)	SV2A	Phase I	UCB Pharma, Belgium (http://www.ucb.com)
	Brivaracetam (UCB 34714)	SV2A	Phase III	UCB Pharma, Belgium (http://www.ucb.com)
Galanin receptors	NAX-5055	GalR1	Preclinical	Neuro Adjuvants Inc., Salt Lake City, UT, USA
Histamine H_3 receptor	Tiprolisant BF-2649	H_3R (receptor)	Phase II	Ferrer International S.A. (http://www.ferrergrupo.com)
Sigma receptor	Anavex 19-144	Sigma-1	Preclinical	Anavex (http://www.anavex.com)
Kainate receptor	LY 300164	–	Preclinical	Eli-Lilly, USA (http://www.lilly.com)
Enzyme modulators				
GTPase dynamin	Bis-tryphostins	–	Preclinical	BioLink, Australia (http://www.bio-link.com)
	Tryphostin A47	–	Preclinical	BioLink, Australia (http://www.bio-link.com)
Adenosine kinase inhibitor	A-134974	–	Preclinical	Abbott Laboratories, USA (http://www.abbott.com)
GABA transaminase	Vigabatrin	–	Recently approved	Lundbeck Inc., USA (http://www.lundbeckinc.com)
P-glycoprotein modulators				
	Celecoxib	P-gp	Preclinical	[38]
	RLIP76	P-gp	Preclinical	[39]

Miscellaneous				
Oxidative stress protectants	Resveratrol	–	Preclinical	[35]
	Curcumin	–	Preclinical	[35]
	Melatonin	–	Preclinical	[35]
Glucose derivative	2-Deoxy-D-glucose	Glycolytic pathway	Preclinical	NeuroGenomeX, Inc, USA (http://www.neurogenomex.com)
Gap junction inhibitor	Tonabersat (SB-220453)	Connexins	Phase II	Minster Pharmaceuticals, UK (http://www.minsterpharma.com)
Unknown	Propylisopropyl acetamide	–	Preclinical	Jazz Pharmaceuticals, USA (http://www.jazzpharma.com)
	Valrocemide	–	Preclinical	Desitin Pharma, Germany (http://www.desitinpharma.com)
	NTP-2014	–	Preclinical	Neurotherapeutics Pharma, USA (http://www.ntprx.com)
	YKP3089	–	Phase II	SK Life Science Inc, Korea (http://pharma.sk.com)
	E2007	–	Phase II	Eisai, USA (http://www.eisai.com)
	Soretolide (D-2916)	–	Phase II	Laboratoires Biocodex, France (http://www.biocodex.com)
	Carabersat	–	Phase II	GlaxoSmithKline, UK (http://www.gsk.com)

this depolarization is reduction in the Mg^{2+} blockage of NMDA receptors, which would promote epileptic activity. Thus, pharmacological inhibition of ASIC might contribute to anticonvulsant action [22].

Hyperpolarization-activated cyclic nucleotide channel modulators

The hyperpolarization-activated cyclic nucleotide (HCN)-gated cation channels are Na^+- and K^+-permeable. Opening of HCN channels produces current, referred to as *I*h, and thus they participate in pacemaker currents in cardiac cells and neurons. These channels are opened by hyperpolarization to negative membrane potentials and by cAMP binding to a consensus cyclic nucleotide-binding domain on the carboxy terminus. A role for HCN channels in epilepsy has been widely proposed, and *I*h is an attractive potential AED target for different types of epilepsy. Because the HCN isoforms have distinctive regional expression patterns and functions, the subunit selectivity of a potential drug might be of significance. Drugs targeting HCN1 might be relevant for limbic seizures, whereas those affecting HCN_2 might be more relevant to absence epilepsy. HCN channel blocker, ZD-7288, inhibits spontaneous epileptiform bursting in the hippocampal slice and confirms the potential of *I*h inhibition as an anticonvulsant approach [23].

Receptor modulators

Synaptic vesicle protein modulators. Synaptic vesicle protein (SV2) is an integral membrane protein present on all synaptic vesicles. One of the isoforms of SV2, designated as 2A, is ubiquitously distributed in the central nervous system (CNS) and is considered to be involved in the regulation of calcium-dependent exocytosis of synaptic vesicles through interaction with a presynaptic protein, synaptotagmin [24]. The AEDs seletracetam and brivaracetam, currently in phase I and phase III of clinical trials, respectively, act by regulating neurotransmitter release after binding to the synaptic vesicle protein 2A.

Galanine receptor modulators. Galanin signaling occurs through three classes of receptors: GALR1, GALR2 and GALR3, which are all part of the G-protein-coupled receptor super family. Galanin is an inhibitor of glutamate but not GABA in the hippocampus; as such, it is capable of increasing the seizure threshold and, therefore, is expected to act as an anticonvulsant [25]. Galanine prototype compounds such as NAX-5055 are under preclinical investigation [26].

Histamine receptor modulators. The identification of histamine H_3 receptors (H_3 Rs) exposed attractive perspectives for the potential therapeutic exploitation of new drug targets. H_3 Rs are mainly localized in the CNS, indicating their function in neurotransmission. The development of selective ligands for these receptors facilitates the elucidation of their physiological and pathophysiological functions. The H_3 R is involved in modulation of neurotransmitter release and is a recognized drug target for neuronal diseases, with some selective H_3 R antagonists (tiprolisant) already in phase II of clinical trials [27].

Sigma receptor modulators. The sigma-1 receptor has recently been identified as a unique ligand-regulated molecular chaperone involved in the modulation of neurotransmitter receptor function and neurotransmitter release. The most prominent action of

sigma-1 receptors is the regulation and modulation of voltage-regulated and ligand-gated ion channels, including Ca^{2+}-, K^+-, Na^+, Cl^- and SK-channels. It also regulates NMDA and IP_3 receptors and is an attractive and potential AED target. The AED anavex, acting through sigma-1 receptors, is in the preclinical stage of development [28].

Kainate receptor modulators. Kainate receptors are non-NMDA ionotropic receptors that respond to the neurotransmitter glutamate. Kainate receptors are involved in excitatory neurotransmission by activating postsynaptic receptors and modulate the release of inhibitory neurotransmitter, GABA, through presynaptic mechanisms [29]. They were identified through their selective activation by the agonist kainate, a drug isolated from the red alga *Digenea simplex* [30].

Enzyme modulators

Inhibitors of the GTPase dynamine. During a seizure, massive, uncontrolled discharges of neurotransmitter caused by exocytosis are followed by synaptic vesicle endocytosis, which retrieves empty synaptic vesicles for re-filling and re-use, perpetuating the seizure and assisting in its spread across the brain. This endocytosis of synaptic vesicles is mediated by a GTPase enzyme, dynamin. Bis-tryphostins and tryphostin A47 are the novel drugs that target dynamin and prevent seizures by inhibiting dynamin-dependent synaptic vesicle endocytosis [31].

Adenosine kinase inhibitors. Another enzyme involved in epilepsy is an adenosine-removing enzyme *viz*. adenosine kinase. Recent research suggests that astrocyte dysfunction, or astrogliosis, a pathological hallmark of an epileptic brain, is associated with upregulation of the adenosine kinase, resulting in focal adenosine deficiency. Thus, adenosine augmentation therapies and adenosine kinase inhibitors such as A-134974 are likely to be effective in preventing seizures and are under preclinical development [32].

GABA-transaminase inhibitors. GABA is an important amino-acid-based signaling molecule in basic neuronal pathways and acts as the major inhibitory neurotransmitter in the CNS. Decrease in brain GABA concentration has been implicated in a variety of neurodegenerative disorders, including epilepsy. One of the ways in which brain GABA concentration decreases is the metabolism of GABA, mediated by the enzyme GABA-transaminase. GABA-transaminase is a potential AED target, and drugs inhibiting this enzyme (vigabatrin and ethanolamine-*O*-sulfate) possess anticonvulsant activity [33].

Oxidative stress protectants

Antioxidant therapies aimed at reducing oxidative stress have received considerable attention in the treatment of epilepsy because excessive release of free radicals caused by oxidative stress is likely to contribute to the initiation and progression of epilepsy [34]. Resveratrol (3,5,40-tri-hydroxy stilbene), a naturally occurring phytoalexin that is present in high concentrations in the skin of red grapes, is a potent neuroprotective. Cell culture studies and studies on animal models suggest that resveratrol mediates its effects mainly via the inhibition of oxidative stress [35]. Another natural antioxidant, curcumin (isolated from *Curcuma longa*) shows antioxidant activity by NO production in the lipopolysaccharide-stimulated microglial cells and prevents microglial-cell-mediated neurodegeneration in neurons [35]. The antioxidant properties of pineal gland hormone, melatonin, are suggested to have an antiepileptogenic role as well [35].

Glucose derivatives

One of the mechanisms by which seizures, occurring as a result of excitability in the brain, can be suppressed is by blocking glycolytic metabolism of sugar. This could be possible by replacing sugar and carbohydrate in the diet with 2-deoxy-D-glucose (i.e. a ketogenic diet). 2-Deoxy-D-glucose also favorably modifies the expression of neuronal genes in the brain that contribute to the adverse consequences of seizures and long-term dysfunction associated with epilepsy [36].

Hormones

The effects of hormones, either peripheral or endogenous, on the nervous system have been well established. Especially, gonadal steroids such as estrogen and progesterone and their precursors have been proven to have direct effects on neurotransmitter receptors. The cyclical changes in these steroids are believed to be important in the pathogenesis of catamenial epilepsy. In addition, endogenous neurosteroid metabolism plays an important part in the growth and maturation of brain. Apart from steroids, erythropoietin is proposed to have a neuroprotective role in several neurological insults [37].

P-glycoprotein modulators

In patients with intractable epilepsy, P-gp, several of the multi-drug-resistant proteins and breast cancer resistance proteins are overexpressed in epileptogenic brain tissue, within brain capillary endothelial cells, astrocytes and neurons. The inability of some epileptic patients to benefit from AED treatment might be due to the effective pumping of these drugs out of the brain and into the systemic circulation, which prevents therapeutic concentrations from being achieved in the brain. Blocking ABC transporters in the brain has been investigated as a possible means of increasing the success of anticonvulsant treatment in these patients. The pumping action of P-gp is inhibited by celecoxib, verapamil and RLIP76/RALBP1. In future, more P-gp will be considered as a major target to reduce the chances of AED resistance for successful long-term therapy [38,39].

The second 'D': delivery systems

Optimal care of patients with epilepsy must include therapies for acute treatment of seizure emergencies, as well as long-term management of seizures. In both situations, an ideal delivery system would direct the drug to the site of action, while limiting exposure elsewhere in the CNS, and the rest of the body [40]. Recognizing that there is no single target to fix, targeted drug delivery has not yet been successfully applied to epilepsy. Antiepileptic therapies aim to correct selective defects, known to occur in a few or many people. This requires numerous approaches that might be effective, although not for everyone. Various novel approaches under development, and/or in the market for the AED delivery, are summarized in Table 2.

Prodrugs

One of the methods by which a drug can be delivered across the blood–brain barrier (BBB) is by making its prodrug. Prodrugs are

TABLE 2

Novel delivery systems of AEDs and their development stages.

Delivery system	Drug candidate	Route of administration	Development stage	Company and web address or Refs
Modified-release delivery systems				
Controlled-release tablets or capsules	Retigabine	Oral	Phase I	Valeant Pharmaceuticals International, USA (http://www.valeant.com)
	Oxcarbazepine (Epliga™)	Oral	Phase III	Supernus Inc., USA (http://www.supernus.com)
	Topiramate (Trokesa™)	Oral	Phase III	Supernus Inc., USA (http://www.supernus.com)
	SPN 802	Oral	Phase II	Supernus Inc., USA (http://www.supernus.com)
	Lamotrigine (Lamictal)	Oral	Recently approved	GlaxoSmithLline, UK (http://www.gsk.com)
	Divalproex sodium (Depakote ER)	Oral	Recently approved	Abbott Laboratories, USA (http://www.abbott.com)
	Carbamazepine (Carbatrol, Microtrol)	Oral	Recently approved	Shire, UK (http://www.shire.com)
Delayed (enteric coated)-release tablets	Divalproex sodium	Oral	Recently approved	Abbott Laboratories, USA (http://www.abbott.com)
Modified-release tablet-in-capsules	Phenytoin sodium	Oral	Recently approved	Mylan Pharmaceuticals, USA (http://www.mylanpharms.com)
Osmotic pumps	Carbamazepine (Tegretol XR)	Oral	Recently approved	Novartis Pharmaceuticals Inc., USA (http://www.novartis.com)
Nanoscale delivery systems				
Polymeric nano- or micro-particles	Thyrotropin	Intranasal	Preclinical	[63]
	Phenytoin	Oral	Preclinical	[64]
	Diazepam	Oral	Preclinical	[46]
	Carbamazepine	Oral	Preclinical	[65]
	Ethosuximide	Parenteral	Preclinical	[66]
Nanocrystals	Lorazepam	Intranasal	Preclinical	Amarin Corporation and Elan Drug Technologies, USA (http://www.amarincorp.com; http://www.elandrugtechnologies.com)
Solid lipid nanoparticles	Diazepam	Oral	Preclinical	[67]
	MRZ 2/576 or probenecid	Parenteral	Preclinical	[68]
	Clozapine	Parenteral	Preclinical	[69]
Magneto-nanoparticles	AMT	Parenteral	Preclinical	[47]
	Ethosuximide	Parenteral	Preclinical	[70]
Liposomes	Valproic acid	Parenteral	Preclinical	[71]
	Superoxide dismutase	Parenteral	Preclinical	[72]
	GABA	Parenteral	Preclinical	[73]
	Amiloride	Parenteral	Preclinical	[74]
Nanoemulsions	Diazepam	Transdermal	Preclinical	[48]
		Intranasal	Preclinical	[49]
	Clonazepam	Intranasal	Preclinical	[50]
	Lamotrigine	Intranasal	Preclinical	[51]
Implants				
Polymeric implants	Adenosine	Intracranial	Preclinical	[52]
	Neuropeptide such as thyrotropic hormone	Intracranial	Preclinical	[53]
	Phenytoin	Intracerebral	Preclinical	[54]
	Phenytoin	Intracranial	Preclinical	[55]

TABLE 2 (*Continued*)

Delivery system	Drug candidate	Route of administration	Development stage	Company and web address or Refs
Bioceramic implants	Valproic acid	Intracranial	Preclinical	[56]
Hybrid cell silicon neural implants	GABA	Intracranial	Preclinical	[57]
Hybrid implants	Diazepam	Extracranial	Preclinical	[75]
	All AEDs (Platform Technology)	Extracranial	Preclinical	[58]
Convection-enhanced delivery systems				
	ω-Conotoxin	Extracranial	Preclinical	[59]
	Botulinum neurotoxins	Extracranial	Preclinical	[60]
	All AEDs (epiCED Platform Technology)	Extracranial	Pre-IND	Medgenesis Inc., USA (http://www.med-genesis.com)
Miscellaneous				
Intranasal	Benzodiazepine	Intranasal	Preclinical	Impax Laboratories, Amarin Corporation plc. and Neurelis (http://www.impaxlabs.com; http://www.impaxpharma.com; http://www.neurelis.com)
	Midazolam (ITI-111)	Intranasal spray	Phase III	Ikano (ITI), USA (http://www.ikanotherapeutics.com)
Rectal	Diazepam (Diastat)	Rectal	Recently approved	Valeant Pharmaceuticals International, USA (http://www.valeant.com)
Gelling suppositories	Carbamazepine	Buccal	Preclinical	[76]
Gene delivery	Biological nano particles for galanine gene transfer	Parenteral	Preclinical	Asklepios Biopharmaceuticals, USA (http://www.askbio.com)
	Adeno-associated virus vector-based gene delivery of neuropeptide Y gene	Parenteral	Preclinical	Neurologix, USA (http://www.neurologix.net)
Inhalation	Propofol	Inhalation	Preclinical	Medkura Inc., USA (http://www.medkura.com)
Transdermal patch	Tiagabine	Transdermal	Preclinical	[77]
Intrathecal pumps	Baclofen	Intrathecal	Preclinical	[78]
Chewable tablets	Carbamazepine	Oral	Preclinical	Taro Pharmaceuticals, USA (http://www.taro.com)
Chewable tablets	Lamotrigine	Recently approved	Preclinical	GlaxoSmithKline, UK (http://www.gsk.com)
Buccal gels	Clonazepam	Oral cavity (between lower gum and lower lip)	Preclinical	[79]
Intra-muscular	Diazepam (Vanquix$^{(R)}$)	Parenteral	Phase III	King Pharma, USA (http://www.kingpharm.com)
Intravenous	Carbamazepine	Parenteral	Preclinical	Lundback Inc, USA (http://www.lundbeck.com)

composed of a drug attached to a distinct compound that is removable via enzymatic cleavage or hydrolysis *in vivo*. The attached moiety can serve to make the prodrug more lipophilic, thereby increasing its tendency to cross the BBB. A prodrug of VPA, DP-VPA, is synthesized by linking VPA with lecithin, a phospholipid, which ensures the inactivation of the parent drug in the systemic circulation. Once DP-VPA reaches the seizure focus, active VPA is released after the cleavage of lecithin by A2 phospholipases, which are overactive at the target site. Another prodrug, fosphenytoin, is made by attaching phenytoin with phosphate ester. The phosphate ester increases the water solubility of phenytoin. When infused into a muscle or into the bloodstream, fosphenytoin is cleaved by naturally occurring alkaline phosphatases to yield active phenytoin. Compared with phenytoin, fosphenytoin can be administered more rapidly through intravenous infusion and is associated with a reduction in discomfort at the delivery site [41]. Studies have shown that the bioavailability of gabapentin is greatly enhanced after oral ingestion of XP13512, an isobutanoyloxyethoxy carbamate prodrug of gabapentin. Enhanced bioavailability was due to carrier-mediated (monocarboxylate transporter type-1 and sodium-dependent multi-vitamin transporter) transport of XP13512 *in vivo* [42].

Modified-release delivery systems

Immediate-release AED formulations have the potential to ameliorate breakthrough seizures when drug levels fall below the minimum effective concentration and cause undesirable side-effects when the levels exceed minimum toxic concentration. Overcoming these problems requires more frequent dosing, but decreased patient compliance might obviate any benefits from frequent daily dosing. Extended-release products permit once- or twice-daily dosing and better control of oral drug release and can accommodate larger doses. The addition of extended-release formulations represents a desire to simplify AED treatment using effective drugs with predictable and manageable side-effect profiles [43].

The extended-release tablet formulation for divalproex sodium (Depakote ER, Abbott Laboratories) is based on polymer matrix technology, wherein contact with water leads to the partial hydration of the outer polymeric layer and subsequent formation of a gel layer that permits a controlled-drug release. When fully hydrated, the outer layer erodes away and drug is released from the tablet. Fluid continues to penetrate towards the tablet core, resulting in a continuous drug release over an extended period. Bioavailability studies also show that extended-release formulation of divalproex produced a lower C_{max} ($P < 0.0001$) and lesser fluctuation in valproate's plasma concentrations ($P < 0.001$) than standard divalproex [44]. Carbatrol technology (Shire Pharmaceuticals) uses three different-sized carbamazepine-filled beadlets (immediate-, extended- and enteric-release) combined in a specific ratio to provide extended release of carbamazepine. Another carbamazepine extended-release formulation (Tegretol XR, Novartis Pharmaceuticals) uses the oral osmotic delivery technology. The tablet comprises an osmotically active component and an opening in the capsule covering for drug release. After administration, fluid expands the osmotically active component, which in turn pushes drug through the capsule opening at a fixed rate. Retigabine (Retigabine MR, Valeant Pharmaceuticals), oxcarbazepine (Epliga™, Supernus Pharmaceuticals), topiramate (Trokesa™, Supernus Pharmaceuticals), lamotrigine (Lamictal-XR, GSK) and phenytoin (Phenytek, Mylan Pharmaceuticals) are a few of the modified-release formulations, which are either in the market or in various stages of development (Table 2).

Nanoscale delivery systems

Another controlled release strategy is to encapsulate the drug in a nanoscale delivery system. Polymeric nanoparticles (NPs) are the most popular, but several other means of delivery have also been studied, including liposomes, nanoemulsions, solid lipid NPs, nanostructured lipid carriers, dendrimers and carbon nanotubes. The use of nanoscale delivery systems such as nanosuspensions, solid lipid NPs and liposomes has led to the solution of various solubility-related problems of poorly soluble drugs, such as benzodiazepine derivatives. Drugs can also be targeted to the brain to enable region-specific delivery and minimize side-effects in other organs. Besides this, depending on their surface charge, surface properties and relative hydrophobicity, NPs can be designed to be used in crossing or penetrating BBBs. In addition, encapsulation of drug in NPs can also provide protection for the drug from *in vivo* degradation and, hence, prolong exposure of the drug by its controlled release [45].

NPs. NPs can be as small as 10 nm and as large as 1000 nm and are typically composed of biodegradable polymers such as poly(-lactic acid), poly(glycolic acid), poly(lactic-*co*-glycolic acid), poly(-alkylcyanoacrylates), poly-ε-caprolactone), poly(methylidene malonate) and polysaccharides. For delivery to the brain, the NPs must be small enough (~50 nm) to travel through the physical restrictions presented by the brain's interstitial space but large enough to enable sufficient drug loading. Size of the NPs can be tailored by altering the NP preparation procedure. In addition, the NP preparation procedure can be altered to encapsulate both hydrophilic and hydrophobic drugs. Once the drugs are loaded into the NPs, they are released through a combination of diffusion and polymer erosion or degradation. Variables such as the molecular weight of the polymer, co-polymer ratio and mechanism of erosion (bulk or surface) affect the rate of drug release, which can vary from a few hours or days to many months. The surface charge of the NPs can also be an important determinant of its effectiveness because neutral or negatively charged surfaces possess a greater volume of distribution when delivered directly into the brain [46]. Currently, magneto-nanoparticles (MNPs) composed of iron oxide and dextran are at the preclinical stage of development. The targeting potential of these MNPs was evaluated on rodent model of temporal lobe epilepsy using nonradioactive a-methyl tryptophan (AMT), covalently attached to MNPs. Magnetic resonance imaging (MRI) studies showed that AMT-MNPs crossed the BBB and concentrated in the epileptogenic tissues. The intraparenchymal uptake of these MNPs was also observed through MRI. Huang *et al.* [47] have also reported core-shell magnetic-field-sensitive NPs capable of delivering AEDs in a controllable manner by tuning the applied magnetic field.

Liposomes. Liposomes are vesicular structures with properties similar to biological plasma membrane: an aqueous core is surrounded by single or multiple bilayers of phospholipids. Liposomes range in diameter from approximately 50 nm to 1 μm. Because of their size, amphiphilic properties and biocompatibility,

liposomes are promising systems for the delivery of AEDs [45]. The unique arrangement of aqueous and lipid components allows for the encapsulation of hydrophilic, amphiphilic and hydrophobic drugs. Liposomes deliver drugs to cells by release of drug into the extracellular space or by liposome entry into the cell. Liposome properties vary substantially with lipid composition, size, surface charge and the method of preparation. To provide the opportunity for stimulus-dependent release of drugs from liposomes, pH-sensitive and temperature-sensitive liposomes have been developed. pH-sensitive liposomes discharge their drug contents in response to an acidic environment, whereas temperature-sensitive liposomes release the encapsulated drug in response to an increase in temperature (to 41–42 °C) applied at the target site. As with NPs, liposomes delivered to the brain can be designed to meet specific requirements of size and charge to provide optimal volume of distribution [45].

Stealth polymers. Although NPs and liposomes are versatile delivery systems, once delivered by intravenous injection, ordinary NPs and liposomes are cleared from the plasma within a few minutes owing to opsonization and subsequent phagocytosis in the reticuloendothelial system. To increase the circulation time, polymers such as poly(ethylene glycol) (PEG), poly-(acrylamide), poly(vinyl alcohol) and polysaccharides have been conjugated to the surface of NPs. The addition of these polymer chains produces what is termed as the stealth character, that is, the particles are no longer opsonized or recognized by the reticuloendothelial system and, therefore, circulate for longer periods. For incorporating stealth character, PEG is the most commonly used polymer. Coating NPs and liposomes with PEG increases their circulation times from several minutes to many hours. The PEG can be incorporated onto the surface of nano-carriers through covalent attachment, adsorption, and physical entrapment or as a copolymer, and the effectiveness of PEG depends on its chain length and surface density, with the latter being more important. Even though the incorporation of stealth character has been shown to increase the circulation time, there is no guarantee that modified NPs and liposomes delivered through intravenous injection will cross the BBB. In addition to stealth polymers, targeting moieties must also be added to the nano-delivery systems to facilitate the penetration of the BBB [45].

Nanoemulsions. Nanoemulsions (optically isotropic and thermodynamically stable systems of water, oil, surfactant and cosurfactant) have been studied as drug delivery systems on account of their solubilization capacity for poorly water-soluble drugs, as well as their enhancement effect on topical and systemic drug availability. For instance, oral microemulsion formulations have been successfully developed for cyclosporine, a highly lipophilic and poorly aqueous-soluble drug, to improve its oral bioavailability and to reduce the variation in absorption profiles. Nanoemulsions have also been considered as a potential delivery system for AEDs such as diazepam, clonazepam and lamotrigine via transdermal and nasal routes [48–51].

Implants

As an alternative to targeted nano-carriers, direct targeting to the seizure focus can be achieved by delivering AEDs directly to the brain parenchyma through an intracranial implant or injection. The other advantages of intracranial administration are bypassing of the BBB and decreased systemic toxicity. Intracranial implants and injections differ with respect to the time course of drug concentrations. Implants can achieve a longer duration of drug exposure owing to sustained release from a matrix, as opposed to injection, which delivers a finite amount of drug at once. Biodegradable polymers have been the most popular type of materials used for constructing drug-releasing implants. Typically, polymers including polyesters, such as polylactic acid, polyglycolic acid and the copolymer, PLGA and polyanhydrides, such as poly[bis(*p*-carboxyphenoxy)propane]-sebacic acid, have been used as intracranial implants for delivering GABA, thyrotropin-releasing hormone and phenytoin. Distance of implant from the seizure focus is an important parameter because degradation and metabolism cause the concentration of drug to drop with distance. Recently, bioceramic materials have been investigated as implantable, sustained-release delivery vehicles for AEDs. López *et al.* evaluated a nanostructured titanium dioxide bioceramic implant containing VPA. The implant was found to deliver drug to the temporal lobe of the brain and shield rats from pentylenetetrazol-induced seizures for up to five months. The bioceramic implant also exhibited biocompatibility and did not cause any damage to proximate neurons. In another study, a titanium dioxide reservoir containing phenytoin was tested, with similar histological results [52–56].

Hybrid cell silicon neural implants. Hybrid cell silicon implants are an *in vivo* therapeutic intervention for neural inhibition of epileptic foci. The device integrates inhibitory neural cells with stimulating electrodes using sol–gel biocomposite materials as the interface. The cells contribute neurotransmitter production and release (GABA), and the electrodes provide a temporal trigger. The efficacy of these implants for seizure inhibition and prevention is yet to be evaluated [57].

Hybrid neuroprosthesis. Subdural hybrid neuroprosthesis (HNP) is an implantable device to treat intractable focal epilepsy. This implant uses localized AED delivery into the epileptogenic zones for seizure control. The subdural HNP monitors the neural activity of the treated epileptogenic zone and delivers the drugs specifically into the cerebral cortical epileptogenic zone transmeningeally, via the subdural space. The feedback-controlled transmeningeal drug delivery permits the post-implantation testing of various AEDs during the course of HNP treatment. Furthermore, the device can accommodate several large-sized drug delivery strips positioned in the subdural space and can deliver AEDs into large, multiple, neocortical epileptogenic zones without spatial restrictions and without using tissue-penetrating catheters or cannulas [58].

Convection-enhanced delivery systems

Convection-enhanced delivery (CED) systems were developed to enhance drug distribution throughout the brain. In CED, a drug solution is gradually infused into a catheter placed locally in the brain's interstitial space, which causes convective and diffusive movement of drug owing to an externally applied pressure. CED provides a way to treat a seizure focus locally, avoiding the BBB and reducing systemic toxicity. CED has been reported to successfully deliver muscimol to the ipsilateral hippocampus and medial temporal lobe. In another *in vivo* study, peptides, conotoxin GVIA and conotoxin MVIIA (N-type calcium channel blocker) elicit anticonvulsant effects when delivered with CED to the basolateral amygdala of kindled rats. The study shows that CED is both safe

and effective for treating seizures. Experimental work, to date, suggests that smaller molecules or molecules with a neutral or negative charge exhibit a larger volume of distribution in the brain when delivered through CED. Drawbacks associated with CED include tissue injury caused by poor placement of catheter within the brain, inadvertent flow of drug solution associated with high pressures and formation of a tissue plug within the catheter outlet, which blocks fluid flow. Recently, microfluidic devices have been developed with a fluid outlet on the side of the device that is perpendicular to the direction of insertion, which decreases the extent of tissue damage and backflow [59,60].

Delivery systems in status epilepticus

Status epilepticus is a serious neurological emergency condition. The goal of treatment is rapid termination of seizure activity because longer the episode of status epilepticus, the more difficult it is to control and the greater the risk of permanent brain damage. Diazepam rectal gel (Diastat-Xcel Valeant Pharmaceuticals, USA), intranasal midazolam (Ikano Therapeutics, USA), intranasal lorazepam in the form of nanocrystals (Amarin Corporation, USA) and intranasal clonazepam (Jazz Pharmaceuticals, USA) offer the prospect of safe, effective and easily administered therapies for seizure emergencies as an alternative to parenteral administration.

The third 'D': devices

One of the most debilitating aspects of epilepsy is the uncertainty of when seizures will strike. For many patients with uncontrolled seizures, the cumulative time spent in seizures is less than one hour per year, yet these individuals are chronically impacted by the uncertainty and fear of their next seizure. Currently, seizures can be controlled in 50–60% of epilepsy patients by drugs and/or surgery, but challenges remain in curing epilepsy in all patients, including the early identification of patients at risk of intractability, accurately localizing abnormal neural activity before seizures in patients with uncontrolled epilepsy, and increasing the specificity of chemical and surgical treatments for epilepsy to maintain or enhance function and minimize or eliminate side-effects. Among these challenges, accurate diagnosis remains a major problem because epilepsy is only a symptom of many disparate causative entities. Currently, electroencephalography (EEG) is the primary tool for monitoring ictal and inter-ictal activity in humans [61]; however, research and development of reliable methods for predicting seizures before they occur and devising treatments are ongoing activities. In the near future, one can envision using a similar device to detect pre-seizure electrical activity and normalize it, either through electrical stimulation or through local drug delivery. Devices for early detection of epilepsy (alerts), diagnosis, surgery and treatment of epilepsy in various developmental stages are summarized in Table 3.

Alert devices

A potential seizure alert system can help epileptic patients with management and emergency treatment during seizure attacks. Many devices are in the various developmental stages or in patients' reach for use as a seizure alert system (Table 3). Epilert is one of the devices designed to alert parents and caregivers of epileptics when an attack begins, especially when the patient is alone and unattended. It consists of a hand- or foot-worn watch-like sensor unit, which detects and processes the specific vibrations of epileptic seizures and transmits an alarm to an alert unit with the parents or caregivers or at a medical control center. It also aids in the monitoring and treatment of patients by providing data and recording epileptic events. Epilert is designed to be very reliable with near-zero false alarms and zero misses. Another epilepsy alert device is the 'Smart Watch' alert. It is a passive, non-intrusive seizure detection device, which provides early detection and alerting to caregivers of epileptic patients prone to tonic–clonic or tonic seizures. These alert devices enable early intervention that can protect the seizing person and improve the quality of patient care because an alert is sent as soon as an attack begins.

Diagnostic and surgical devices

When AEDs fail to control seizures or if AEDs are associated with unacceptable side-effects, excisional brain surgery is an alternative treatment approach. The surgical intervention involves removal of minimal amount of brain tissue necessary to render the patient free from their seizures with little to no additional neurological deficit. In epilepsy, before surgery, diagnosis is crucial and should be confirmed by a professional. Confident diagnosis in all cases of seizures is difficult because seizure types vary, unusual behavior and blank spells might not be recognized as seizures, there might be no accompanying neurological signs, and if an eyewitness is lacking, the diagnosis might not be made at all.

The physiological signature of epilepsy is that during a seizure, a network of neurons in the brain becomes abnormally excitable and synchronized. Monitoring the resultant electrical discharge forms the basis of diagnosis, and for over 50 years, EEG was the only method of monitoring functional activity in the brain. In the past few years, new imaging techniques for measuring brain function are available. Magnetoencephalography offers considerably better spatial resolution than EEG without any loss of temporal resolution. Through MRI, different anatomical locations of cerebral functions and inter-ictal epileptic discharges could be imaged. Results have demonstrated that MRI, coupled with magnetically susceptible NPs improves the ability to image functional regions of the brain and better identification of epileptic regions. Single-photon emission computed tomography (SPECT) and laser-induced interstitial thermotherapy enable imaging of seizure-affected areas of brain. More recently, non-invasive optical methods to detect hemodynamic changes associated with seizures are in use. Diffuse optical imaging is a non-invasive technique with good specificity because it directly measures the cerebral hemodynamics [62]. It probes the head 2–3 cm down from the scalp and provides a functional image with approximately 5 mm resolution. In addition, it can be developed into a portable device, such as Optic Holder, and used for long-term and ambulatory monitoring to record multiple seizure events. It is sensitive to global interference, however, such as that from scalp and skull.

Brain stimulation devices

Brain stimulation is a kind of physical method for pharmacoresistant epilepsy treatment. The first FDA-approved extracranial brain stimulation device was the Vagus Nerve Stimulation therapy system developed by Cyberonics Inc. Other extracranial systems, such as trigeminal nerve stimulation, repetitive transcranial magnetic stimulation and transcranial direct current stimulation are in

TABLE 3

Novel devices for management of epilepsy, their applications and development stages.

Device	System	Application	Developmental stage	Company and web address or Refs
Devices for epileptic alerts				
Epilert	Mobile-phone-based device	Seizure Alert	In market	BioLert Ltd., Israel (http://www.biolertsys.com)
Epdetect	Mobile-phone-based device	Advanced signal-based seizure detection	In market	ImpediGuide Ltd., Israel (http://www.epdetect.com)
Accelerometer	Wearable device	Algorithm-based seizure detection	Preclinical	ImpediGuide Ltd., Israel (http://www.impediguide.com)
Medpage ST-2	Wearable device	Monitor and detect convulsions	In market	Medpage, UK (http://www.medpage-ltd.com)
SeizAlert	Wearable device	Forewarn impending epileptic seizure	Phase II	Hercules Development Corp., USA (http://www.csiir.ornl.gov)
SmartWatch Alert	Watch-based device	Detection and alerting device	Phase III	IntelliVision, USA (http://www.intelli-vision.com)
BrainGate™ Neural Interface System	Sensor implant device	Sensing electrical activity	Preclinical	BrainGate, USA (http://www.cyberkineticsinc.com)
NeuroPort System	Software-based multichannel sensor device	Record and monitor brain electrical activity	Recently FDA approved	Cyberkinetics, Inc., USA (http://www.cyberkinetics.com)
Devices for diagnosis				
Advanced EEG	–	Electrical spikewave monitoring in brain	In market	Electrical Geodesics, Inc., USA (http://www.egi.com)
Diffuse optical imaging	OpticHolder	Seizure detection and prediction	Preclinical	[62]
Devices for surgery				
Magnetoencephalography	–	Recognize paroxysmal discharge	In market	VSM MedTech Ltd., Canada (http://www.vsmmedtech.com)
Functional MRI	–	Mapping of areas with increased blood flow and localization of epileptogenic zones	In market	Kappametrics Inc., USA (http://www.kappametrics.com)
High-resolution brain SPECT	–	Identification of hypo- and hyper-metabolic regions	In market	NeuroLogica Corporation, USA (http://www.neurologica.com)
Diffusion tensor imaging and tractography	–	Localization of lesions for improved surgical intervention	Preclinical	[61]
SIGFRIED (Signal Modelling For Real-Time Identification And Event Detection)	–	Real-time functional mapping using electrocorticography	Preclinical	[80]

NIRS (Near-infrared spectroscopy)	–	Measures hemodynamic changes associated with neural activity	In market	TechEn, Inc., USA (http://nirsoptix.com)
Gamma knife	–	Radio surgery to destroy cells causing seizure activity	Preclinical	[81]
Devices for brain stimulation				
Extracranial systems				
Vagus Nerve Stimulation	Implant device	Reduces hyper-excitability in seizure-generating networks by applying extrinsic stimulation	In market	Cyberonics, Inc., USA (http://www.cyberonics.com)
Focal cooling and uncaging	Implant device	Cooling diminishes paroxysmal bursting	Pivotal studies	[61]
Trigeminal nerve stimulation	Implant device	Stimulation of the trigeminal nerve bilaterally to stop seizures	Pivotal studies	[82]
Repetitive Transcranial Magnetic Stimulation	Implant device	Seizure suppression by externally applying magnetic stimulation	Pivotal studies	The Magstim Company Ltd., UK (http://www.magstim-us.com)
Transcranial Direct Current Stimulation	Implant device	Seizure suppression by generating electromagnetic field through weak electrical currents	Pivotal studies	The Magstim Company Ltd., UK (http://www.magstim-us.com)
Intracranial systems				
RNS System (Responsive Neurostimulation)	Implant device	Termination of epileptic activity by inhibitory polarization produced by slow intermittent electrical stimulation	Pre-market approval application to USFDA	NeuroPace Inc., USA (http://www.neuropace.com)
DBS (Deep brain stimulation)	Implant device	Stimulation of discrete networks close to seizure generator	Submitted pre-market approval application to USFDA	Medtronic Inc., USA (http://www.medtronic.com)
Miscellaneous devices for overall epilepsy care				
Rehabilicare	Cortical stimulators and mapping systems	Occupational and rehabilitation support of epilepsy associated-physical impairment	In market	Integra Life Sciences Corporation, USA (http://www.integra-ls.com)
Safety Place Mat®	Working mats	Protect the head, face or chin during epileptic attacks	In market	Otoko Enterprises Inc., USA (http://www.seizuresupport.com/products.htm)
Protective Headwear's	Wearable	To protect the head, face or chin during epileptic attacks	In market	Plum Enterprises Inc., USA (http://www.plument.com)

TABLE 4

Software to support epilepsy care, their applications and development stages.

Software	Application	Development stage	Company and web address or Refs
IdentEvent™	Algorithms to achieve accurate seizure detection, EEG recording and analysis	In market	Optima Neuroscience Inc., USA (http://www.optimaneuro.com)
NeuroScore	Seizure detection and video synchronization	In market	Data Sciences International (DSI), USA (http://www.datasci.com)
Neural Network Models With Adaptive Activation Function (NNAAF)	To detect epileptic seizures	Research	[83]
RecogniZ'e	Computer-aided seizure detection	In market	BrainZ Instruments Limited, New Zealand (http://www.brainzinstrumentsltd.com)
Net Station 4.3	Acquisition and physician review and synchronized video for extended monitoring	In market	Electrical Geodesics Inc., USA (http://www.egi.com)
SPM 8	Software based application for EEG/fMRI	In market	Wellcome Trust Centre for Neuroimaging, London, UK (http://www.fil.ion.ucl.ac.uk/spm/software/)
Neuroport Software System	Multichannel system for recording human brain and peripheral-nerve electrical activity	In market	Blackrock Microsystems, USA (http://www.blackrockmicro.com)
iPlan® Net	BrainLAB, a flexible planning solution that gives the freedom to choose exactly how, when and where to plan treatments for epilepsy chronic therapy	In market	BrainLAB AG, Germany (http://www.brainlab.com)
eemagine EEG	EEG data analysis	In market	ANT B.V. (Advanced Neuro Technology), Netherlands (http://www.ant-neuro.com)
Leonardo Brainmap	EEG recording, analysis and monitoring	In market	Dr. SAGURA Medizintechnik, Switzerland (http://brainmap.sagura.royalmedicalsystems.com)
Epilexia	Diagnostic tool for those with suspected epilepsy based on clinical data	In market	(http://www.doctorslounge.com/neurology/downloads/epilepsy/Epilexia.htm)
NeuroGuide Deluxe QEEG 2.5.5	Informative and comprehensive conventional EEG and QEEG analysis	In market	Applied Neuroscience, Inc., USA (http://www.appliedneuroscience.com)
Epivista	Electronic calendar that includes the medical record for seizure sufferers	In market	Desitin Pharmaceuticals, GmbH, Germany (http://www.epivista.com)
EpiTrax	Advanced seizure diary software program designed to track and analyze every pertinent detail surrounding seizures, medication and possible seizure triggers	In market	NeoMed Software, LLC, USA (http://www.neomedsoft.com)
TWin®	Windows-based EEG and PSG software for monitoring physiological signals	In market	Grass Technologies, an Astro-Med Inc., USA (http://www.grasstechnologies.com)
Photosensitive Epilepsy Analysis Tool (PEAT)	To identify seizure risks in web content, TV programmes and software	In market	The Board of Regents of the University of Wisconsin System, USA (http://trace.wisc.edu/peat/)

early-stage clinical testing. Two intracranial electrical stimulation systems, the Responsive Neurostimulation System™ (Neuropace) and the Intercept™ Epilepsy Control System (Medtronic) are in late-stage clinical testing. Other intracranial treatment systems utilizing cooling or other forms of non-electrical energy are in early development stages. The relative advantages and disadvantages of each of the approaches are discussed in Table 3. Overall, the anticonvulsant efficacy obtained with physical approaches is relatively low and results in moderate reduction in seizure frequency. Furthermore, in contrast to drug trials, traditional placebo-controlled trials are not practical with these devices.

Software

Software aids help to provide accurate seizure alert support and faster analysis of neurological abnormalities. Some of the software which is in patients' hands, ranging from emergency mobile phone alerts to high-tech seizure pattern analysis tools, are shown in Table 4.

Future prospects

A broad range of strategies to stop seizures is currently being investigated, with various modes of control and intervention. For medication-resistant epilepsy, devices such as those discussed above present an exciting new avenue to help patients when AEDs have not markedly reduced seizure burden. However, new generation AEDs, delivery systems and antiepileptic devices are currently in pivotal stages of clinical trials and are showing considerable promise. Motivated by this success, the field is poised to produce more advanced three 'D's that can track seizure generation in epileptic networks and trigger drug delivery at seizure foci to prevent epileptic attacks or clinical events. The evolution of engineering technology as applied to epilepsy presents renewed promise that the probability of seizure onset can be identified and responsive therapy delivered to prevent epileptic events from occurring. Much of this progress has been stimulated by recent technological advances at a variety of temporal and spatial levels, including cell and gene therapies, genetic mapping, and the use of stem cells in epilepsy. The initial results with these technologies are exciting, but considerable development and controlled clinical trials will be required before these treatments earn a place in our standard of clinical care. Ultimately, the success of epilepsy treatment and management rests upon collaboration between neuroengineers, formulation scientists, clinicians and industrialists to adapt new technologies for clinical use.

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