**ABSTRACT**

**Introduction**: Epilepsy is one of the most serious neurological conditions, affecting almost 50 million people around the world. Despite more than 20 antiepileptic drugs (AEDs) available, seizures are still uncontrolled in one third of patients.

**Areas covered**: The present paper reviews current compounds in preclinical and clinical development for the treatment of focal epilepsies and new potential molecular targets recently identified.

**Expert Opinion**: 1OP-2198, Cannabidavirin, Everolimus, FV-082, Ganaxolone, Minocycline, NAX 810-2, Padsevonil and Selurampanel seem to be particularly promising in focal epilepsy. Some of them, Everolimus and Ganaxolone, are already completing Phase III development while others are still at a preclinical stage. Everolimus represents the first example of precision-medicine in epilepsy and the first generation of disease-modifying agents but data on long term safety are needed. Among AEDs in Phase II development, Cannabidavirin, Padsevonil and Selurampanel may represent a promising fourth generation of compounds for focal epilepsies if they successfully proceed to subsequent stages. Data on general tolerability, effects of cognition and behaviour as well as the potential for interactions in polytherapy will be key element for the success or decline of these drugs.

**Key words:** epilepsy, antiepileptic drugs, 1OP-2198, Cannabidavirin, Everolimus, FV-082, Ganaxolone, Minocycline, NAX 810-2, Padsevonil, Selurampanel

1. **BACKGROUND**

 Epilepsy is a serious neurological disorder affecting approximately 50 million of people worldwide [1]. In high-income countries, incidence rates range between 40 and 70/100,000 persons/year, with higher rates among children and elderly people [2]. Incidence rates are much higher in resource-poor countries, being above 120/100,000/year, but even in high-income countries, poor people seem to have a higher incidence [3].

According to the World Health Organization, epilepsy accounts for about 0.5% of the global burden of all diseases with total annual costs, in Europe, of approximately 15.5 billion Euros [4]. In May 2015, the World Health Assembly approved the WHO Resolution on the Global Burden of Epilepsy which provides a powerful tool to engage national governments into implementing effective actions to improve medical and social services for people with epilepsy, promoting public awareness about epilepsy and allocating resources to epilepsy research [5].

1. **MEDICAL NEED**

 Treatment outcome studies in epilepsy show that one third of patients are controlled on a single antiepileptic drug (AED), another third requires a combination of two or more drugs to be seizure free, while, in the remaining third, chances of becoming seizure free are considerably low and these patients have uncontrolled seizures lifelong [6]. For this reason, during the last 30 years, a number of new drugs have been marketed almost every year, leading to a considerable number of drug options and combinations. Nevertheless, improvements in terms of clinical outcome have clearly fallen expectations with no significant changes in the proportion of seizure free patients [7].

The definition of drug-resistance proposed by the International League Against Epilepsy (ILAE) has introduced the concept of sustained seizure freedom which represents the only efficacy outcome measure consistently associated with improved quality of life [8]. Using this measure, a systematic review and meta-analysis of placebo-controlled studies of AEDs has pointed out that the overall pooled-risk difference in favour of new AEDs compared with placebo is only 6% (95% CI 4%-8%) with a number needed to treat (NNT) of 16 [9]. It appears, thus, evident that further research is needed and new drugs are more than warranted.

This review article aims to provide a comprehensive overview of novel compounds that are currently under investigation at a preclinical and clinical stage for the treatment of focal epilepsy. References were identified by searches of Medline/PubMed and on clinicaltrials.gov. The reference list of relevant articles was also hand-searched for additional publications (e.g. book chapters or review papers) if relevant for the discussion.

1. **EXISTING TREATMENT**

 AEDs can be currently divided into three generations of compounds. This distinction is mainly based on the chronological order these drugs have been marketed but it also reflects the evolution of pharmacology of AEDs. In fact, first generation AEDs (i.e. Barbiturates, Phenytoin, Carbamazepine and Valproate) followed the discovery of animal models of epilepsy. Lamotrigine, Oxcarbazepine, Topiramate, Tiagabine, Levetiracetam, Zonisamide and Pregabalin can be considered second generation AEDs and followed the identification of different molecular targets in neuronal transmission. Finally, drugs marketed during the last 10 years (i.e. Lacosamide, Ruifinamide, Eslicarbazepine acetate, Retigabine, Brivaracetam and Perampanel) are regarded as third generation drugs because some of them (i.e. Eslicarbazepine and Brivaracetam) are structurally related to pre-existing AEDs and others (i.e. Rufinamide, Lacosamide, Retigabine and Perampanel) have new mechanisms of actions [10]. In the North American literature, Clobazam and Vigabatrin are sometimes included in this list while, in the European literature, they are considered second generation AEDs.

Despite some of these drugs may have shown some advantages in terms of pharmacokinetics, potential for interactions and tolerability [11], the proportion of drug-resistant patients remains dramatically unchanged and patients on polytherapy still present with often unacceptable medication-related side effects [7]. The reason for that is easily understandable as all these three generations of compounds have focused basically on the same neurobiological targets, namely voltage-dependent ion channels, direct modulation of GABAergic and glutamatergic neurotransmission.

1. **CURRENT RESEARCH GOALS**

 Current pharmacological research in epilepsy is focusing on new potential targets and the advances in neurobiology and molecular pharmacology of epilepsy are bringing into the epilepsy field previously unexplored neurochemical pathways such as adenosine and galanin. Among classic neurobiological targets, like GABA and AMPA receptor modulators, a few new compounds are currently under investigations. Finally, for the first time, potential disease-modifying agents such as mTOR inhibitors or minocycline are under development.

1. **SCIENTIFIC RATIONALE**
	1. **Cannabis derivatives**

 The potential use of the Cannabis plant in medicine has a long story dating back to centuries ago but the first modern description of the use of a cannabis-based product for the treatment of epileptic seizures was published in 1843 by O’Shaughnessy who investigated the effect of *Cannabis Indica* in patients with different disorders including epilepsy [12,13]. Subsequently, William Gowers mentioned the potential effect of *Cannabis Indica* in patients with bromide-resistant seizures [14].

The biological activity of cannabinoids is mediated by cannabinoids receptors type 1 (CB1) and type 2 (CB2) which belong to a family of Gi/0-coupled receptors widely distributed in the central nervous system (CNS) with CB1 mainly in neurons while CB2 in the microglia and in the immune system [12]. CB1 receptors are mainly expressed pre-synaptically in GABAergic and glutamatergic neurons and the activation of these receptors result in inhibition of synaptic neurotransmission [15]. The well-known psychoactive effect of tetrahydrocannabinol (THC) seems to be mostly mediated by CB1 receptors which seem also to mediate some of the anti-seizure effects [15]. However, the psychotropic effect of THC has always been a barrier to a potential use in epilepsy and, for this reason, modern cannabinoid research focused only on non-psychoactive agents and two specific compounds, namely Cannabidiol (CBD) and Cannabidivarin (CBDV), are currently under development [12].

* 1. **Neurosteroids**

 The term “neurosteroid” originated in the 1980’s and refers to a class of endogenous steroids synthesized from cholesterol in the CNS that are potent and effective allosteric modulators of GABA-A receptors [16]. However, their effect on GABA-A receptors is different from other GABA agents as they interact both synaptically and extrasynaptically and at a binding site different from that of benzodiazepines [17]. All these elements have made neurosteroids particularly attractive for the treatment of refractory status epilepticus as GABA-A receptor internalisation and functional inactivation are claimed to be among the main neurobiological explanations for poor response to benzodiazepines in refractory status [18]. In addition to that, a number studies seem to suggest that the effect of neurosteroids goes beyond the simple interaction with GABA-A receptors, preventing plastic changes in the limbic system induced by stress [19]. For this reason, neurosteroids are currently investigated in epilepsy especially for the treatment of drug-refractory status but also in mood and anxiety disorders [20].

Even if experimental data on neurosteroids are promising, the low aqueous solubility and poor oral bioavailability represent significant limitations for almost all compounds belonging to this class [21]. Other potential complicating issues with this class of drugs include possible endocrine effects via actions on intracellular (hormonal) steroid receptors which need clarification [19]. Ganaxolone is one of the main drugs currently under development for focal epilepsies. Other neurosteroids are under investigations just for status epilepticus.

* 1. **mTOR inhibitors**

 Rapamycin (sirolimus) and derivative compounds (rapalogues) like everolimus, temsirolimus, deforolimus and ridaforolimusm target a group of serine/threonine protein kinases (mTOR) that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription [22]. Dysregulation of mTOR pathways have been implicated in the development and progression of a number of conditions including type-2 diabetes, inflammation, cancer and cardiovascular disease [22]. In the brain, excessive activation of mTOR signalling leads to altered cortical architecture, abnormal neuronal morphology and growth, and a number of neurological conditions have been linked to mTOR signalling pathways including not only epilepsy but also Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, major depression and schizophrenia [23].

In the context of epilepsy, there are now a number of so-called mTORopathies-related epilepsies which include tuberous sclerosis complex (TSC), focal cortical dysplasia (FCD), ganglioglioma, hemimegalaencephaly [23]. All these conditions share common histopathological features, namely astrogliosis, cortical dyslamination and dysplastic neurons.

mTOR forms two different complexes mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) and mTOR inhibitors target predominantly mTORC1 [24]. mTOR inhibitors, like everolimus, have shown to prevent abnormal cell growth and restore cell size and morphology and for this reason they are increasingly considered disease-modifying agents in mTOR-related epilepsies like TSC [23]. In addition to that, everolimus seems to directly inhibit seizure activity in several animal models of epilepsy but the exact mechanism of action is still unclear [20].

* 1. **Adenosine**

 Adenosine is an endogenous metabolite and a ligand of a G-protein coupled receptor family. Adenosine is not a classically released neurotransmitter, although it acts on pre-synaptic and post-synaptic receptors. In fact, adenosine seems to be a powerful homeostatic bioenergetics network regulator [25], restoring homeostasis through receptor-dependent and independent effects.

In vitro studies have shown that tissue content of adenosine rises rapidly after seizure initiation and this is thought to be a feedback mechanism to limit seizure activity [25]. Studies in animal models of epilepsy have shown that A1 receptor agonists are not only anticonvulsants but also augment the effect of standard AEDs [26] while selective A1 receptor antagonists not only worsen seizures but seem to blunt the effect of AEDs [27]. Interestingly, adenosine receptors are also expressed by a number of cells involved in inflammation processes [28] and a number of studies have discussed the role of inflammation in epileptogenic mechanisms [29]. For all these reasons, adenosine is seems to be a promising target to restore the balance balance between excitation and inhibition without interfering post-synaptically with GABA or glutamate receptors.

In adults, the amount of adenosine in the brain is regulated by the adenosine kinase (ADK), which is expressed by astrocytes [25]. Following a brain insult, astrocytic ADK expression undergoes a biphasic response, namely an acute down-regulation within hours followed by astrogliosis and ADK overexpression within days or week [30]. A number of animal models of epilepsy showed ADK upregulation and adenosine deficiency in the epileptogenic sclerotic tissue [30]. Given all these findings, it appears evident that the scientific rational for the development of ADK inhibitors in epilepsy is quite strong. In fact, these agents would be able increase the levels of endogenous adenosine and to potentiate the already described adenosine response.

* 1. **Galanin receptors**

 Galanin was first identified more than 30 years ago as a neuropeptide acting primarily as a modulator of neurotransmission in the brain and the peripheral nervous system but over time it became evident that galanin and other galanin family peptides have a number of additional non-neuronal actions such as on glia, endocrine cells, energy homeostasis and paracrine effects on bones [31]. A number of studies in animal models of epilepsy have shown that galanin is implicated in epilepsy. In the self-sustaining status epilepticus (SSE) model, hippocampal areas are galanin depleted after stimulation of the perforant path dentate gyrus pathway [32] and the duration of the SSE can be markedly shortened by injection of galanin into the dentate hilus [31–33]. The anticonvulsant effect of galanin seems to be mediated by GalR1 and GalR2 receptors but the use of Galanin itself has been limited by poor metabolic stability and lack of blood-brain penetration [31]. Among different potential galanin receptor agonists, those acting on GalR1 receptors have been rapidly excluded as GalR1 receptors also inhibit the release of insulin leading to poor tolerability and many systemic effects [20,31]. GalR2 receptors seem to be localised just on the CNS and, interestingly, their stimulation seem to reduce glutamate release [34], further suggesting a promising anti-seizure activity for this class of compounds.

* 1. **Potassium channels**

 Potassium channels are ubiquitous in neuronal and glial cell membranes and they are central to excitability [35]. Among all voltage-gated potassium currents, the M-current has been historically linked to epilepsy with the discovery of benign familial neonatal seizures, a rare autosomal dominant condition associated with mutations of KCNQ subfamily genes [36]. Retigabine is the prototype of potassium channels openers and represents the first in-class AED marketed so far. It is a structure analogue of Flupirtine, a centrally acting nonopioid analgesic with also muscle relaxant and neuroprotective properties [37,38]. It was already known since the 1980s that Flupirtine had some anticonvulsant activity and its subsequent structure-activity optimization let to the development of Retigabine [39]. In 2013, shortly after having been marketed, GlaxoSmithKline (GSK) announced that there were safety issues with the drug as it could cause blue discoloration of the skin and eye abnormalities. As a consequence, GSK decided to discontinue the production of Retigabine in 2017. However, research on the potential role of potassium channel openers is epilepsy has progressed with the identification of other potential drugs like 1OP-2198.

1. **COMPETITIVE ENVIRONMENT**

**6.1 Cannabis derivative**

 CBD and CBDV are both active constituents of *Cannabis Sativa* and both of them have shown antiepileptic activity in both in vitro and in vivo models of epilepsy [20,40]. Interestingly enough, none of them interact with CB receptors and/or the endocannabinoid system [20,41] and both of them seem to modulate intracellular calcium in order to maintain a normal neuronal function [20,42], though a specific target hasn’t been identified yet.

CBD is probably the most popular cannabinoid at the moment [43]. It has already received orphan drug designation from the Food and Drug Administration (FDA) for infantile spasms in Dravet syndrome, Lennox-Gastaut syndrome and Tuberous Sclerosis Complex (TSC) and it is under Phase III development for these indications with GW Pharmaceuticals. CBDV has shown anticonvulsant activity in a broad range of animal models including the mouse maximal electroshock seizure (MES) model of generalised seizures, the mouse audiogenic model and the acute pentylentetrazole (PTZ) rat model [20]. It has also shown some antiepileptiform activity in the 4-aminopyridine model but no effect against pilocarpine-induced seizures, though these seizures were significantly attenuated when administered with valproate or phenobarbital [44]. Preclinical safety, pharmacology, genetic and toxicology studies of CBDV have been conducted showing no target-specific toxicology. Phase I pharmacokinetic studies showed that both oral and intravenous formulations were well tolerated with dose proportional plasma concentration-time curve and Phase IIa studies in small samples of patients with drug-resistant focal seizures are now completed (NCT02369471, NCT02365610). CBDV has also conducted a Phase IIa for the adjunctive treatment of focal seizures in adult patients (18-65 years) starting at 400 mg twice daily titrated up to 800 mg twice daily [20]. However, a press release announced that CBDV did not meet its primary endpoints. The trial was conducted outside the United States, primarily in Eastern Europe, and the extent of the placebo response was substantially greater than that seen in published studies of other treatments in similar patient populations [45].

**6.2 Neurosteroids**

 Neurosteroids under investigations in the context of epilepsy include Ganaxolone, SAGE-217, SAGE-689 and SAGE-547 but Ganaxolone is the only one under investigations for the treatment prophylactic treatment of seizures while the other are mainly under investigation for status epilepticus.

Ganaxolone is a positive allosteric modulator of GABA-A receptors. It is a synthetic analogue of allopregnanolone (progesterone metabolite) in order to have the same effect of allopregnanolone on GABA-A without the activation of nuclear progesterone receptors. Ganaxolone is currently under investigations for focal epilepsies but also as orphan indication in status epilepticus, genetic epilepsies, anxiety and fragile X syndrome. It is being developed in three different formulations (intravenous, capsule and liquid suspension). Marinus Pharmaceuticals completed a 10-weeks Phase II trial of Ganaxolone 1500 mg/day as adjunctive treatment in 147 patients with drug-resistant focal epilepsy showing a 18% decrease in mean weekly seizures [20]. In terms of tolerability, pool data from Phase I and Phase II studies show that most adverse events are mild to moderate in severity and reversible on drug withdrawal. No fatalities reports disclosed (to date >1300 patients exposed). Common adverse events in Phase II trials include dizziness, fatigue and somnolence in 13%-16% patients with discontinuation due to adverse events in 7% [20]. A Phase III, randomised, double-blind, placebo-controlled trial followed by long-term, open-label extension phase in adult patients with focal epilepsies is now terminated (NCT01963208, NCT02519439) but results are not available yet.

**6.3 mTOR inhibitors**

 Everolimus has been already approved for the treatment of patients with TSC who have subependymal giant cell astrocytomas and renal angiomyolipomas. A Phase III, randomised, double-blind, placebo-controlled study investigating the efficacy and tolerability of Everolimus as adjunctive treatment in patients with TSC aged 2-69 and partial onset seizures (NCT01713946) has been conducted and results have been already published [46]. The study showed that high-exposure Everolimus (9-15 ng/mL) is associated with a median percentage reduction in seizure frequency of 39.6% as compared to 29.3% with low-exposure Everolimus (3-7 ng/mL) and 14.9% with placebo [46]. The open label extension phase is currently running (NCT02962414). A study investigating the antiepileptic efficacy of Everolimus in patients with Focal Cortical Dysplasia Type II and drug-resistant seizures is planned (NCT03198949).

**6.4 Adenosine**

 According to their chemical structure, ADK inhibitors can be classified in nucleoside and non-nucleoside ADK inhibitors. The prototype of nucleoside ADK inhibitors is 5-iodotubercidine and its analogues. Although these compounds showed to inhibit seizures in the MES model in rats [47], none of them met a safety and efficacy profile for further drug development. In general terms, the majority of ADK inhibitors are limited by severe toxicity including liver toxicity, cardiovascular problems and brain haemorrhage. In 1996, a Phase I study in humans for a specific compound, namely GP-3269, was announced by the US company Gensia Inc. but results are not available [30]. There are ongoing plans to use a newly developed drug-screening platform to identify compounds from a new class of ADK inhibitors [20].

**6.5 Galanin receptors**

 NAX 810-2 was synthesized by PolyPeptide Laboratories (San Diego, CA). It is a GalR2 preferring agonist which showed to be effective in protecting against seizures in animal models of epilepsy like the 32 mA, 6Hz and corneal kindling models [40,48]. NAX 810-2 did not show to elevate blood glucose levels as compared to GALR1 preferring compounds, but it seems to have a broad receptor activity interacting also with urotensin II, alpha2c adrenergic and angiotensin I receptors. The clinical relevance of these findings in terms of tolerability is still unknown. Studies in rats and non-human primates are planned.

**6.6 Potassium channels**

 1OP-2198 is currently under development for 1sr Order Pharmaceuticals. It is a highly selective second generation Kv7 (KCNQ) potassium channel opener and it has shown anticonvulsant properties in a variety of animal models including the MES, PTZ, bicuculline and 6HZ [20] models. It seems to have a pharmacological profile similar to that of Retigabine but with greater potency. A human study in healthy volunteers is planned in order to evaluate pharmacokinetics and tolerability at a starting dose of 5 mg [20]. Further studies in monkeys, rats and rabbits are planned to support further trials in humans and to advance studies in the paediatric population [20].

**6.7 Other Compounds**

 FV-082 is currently under development for Flurinov Pharma. Preclinical studies suggest a broad spectrum potential for both focal and generalised seizures but the mechanism of action hasn’t been clarified yet. FV-082 seems to interact with a number of targets from ion channels to androgen receptors and monoamininoxidase B [20].

 Minocycline is a highly brain penetrant tetracycline with anti-inflammatory, immunomodulatory and antiapoptotic properties [20,40]. It has shown anticonvulsant properties in a number of animal models including the 6-Hz seizure model, amygdala-kindled rats and the pilocarpine-induce status [49–51]. Open label studies have been conducted in Angelman syndrome and fragile X syndrome but no rigorous Phase II trils are available.

 Padsevonil is a new pre- and post-synaptic inhibitor currently under investigation for UCB for patients with drug-resistant epilepsy [52]. A Phase I pharmacokinetic study (NCT03480243) and Phase IIa randomized, double-blind, placebo-controlled, dose finding studies to evaluate the efficacy and safety of Padsevonil as adjunctive treatment of focal seizures in adult are currently running (NCT03370120, NCT03373383).

 Selurampanel is a competitive antagonist of glutamate AMPA and kainate receptors. A Phase II, 12-week, randomized, double-blind, placebo-controlled, exploratory dose-titration study was carried out by Novartis in 93 patients with drug-resistant focal epilepsy (NCT01147003). Mean percentage change from baseline seizure frequency was 39% for patients randomized to 450 mg/daily, 22% for patients assigned to 300 mg daily and 24% for patients treated with placebo [52]. The open-label, extension phase of the study has also terminated (NCT01338805) but results are not available yet.

1. **POTENTIAL DEVELOPMENT ISSUES**

 The discovery of new potential targets for the treatment of epilepsy is obviously promising as three generations of AEDs acting on the same targets did not change the proportion of drug-resistant patients. However, new mechanisms of action may also be associated with new adverse events and, for this reason, data on safety will be crucial in all phases of development for these drugs.

It is now established that adverse events play a major role on quality of life of patients with chronically unremitting epilepsies [53] and even if seizure freedom is achieved, if this is at the expenses of unacceptable side effects, quality of life remains poor [54].

Common or very common side effects, meaning with a prevalence >1%, should be easily identified during premarketing development but rare idiosyncratic reactions may need larger populations of exposed subjects to be identified. It is already known that some AEDs may be associated with serious idiosyncratic reactions that, in some selected case, can be even life-threatening such as Stevens-Johnson syndrome or toxic epidermolysis, pancreatitis, hepatitis and bone marrow aplasia [53]. Careful clinical monitoring will be needed even if some these compounds will successfully go into post-marketing Phase IV.

The potential effect of AEDs on cognition and behaviour is another relevant issue. Cognitive slowing, sedation or somnolence can occur, at a different extent, with almost all AEDs [55]. Psychiatric adverse events seem to occur in about 8% of people with drug-resistant epilepsy independently on the mechanism of action but some patients seem to be more vulnerable than others [56]. Data on cognitive and behavioural safety of these new compounds will be crucial in Phase III development.

1. **CONCLUSIONS**

A number of new molecular targets have been identified and compounds currently under development are promising. Everolimus and Ganaxolone are those at an already advanced development stage followed by Cannabidavirin, under Phase IIb, and Padsevonil and Selurampanel under Phase IIa. Other drugs are at a very early stage of drug development and further data in humans are needed.

Further studies in refractory status epilepticus in children are warranted [57].

1. **EXPERT OPINION**

 AEDs marketed during the last few decades focused on a limited number of already known molecular targets, namely direct modulation of GABA or glutamate receptors and voltage-gated channels. It is, therefore, evident that drugs acting on new targets are of particular interest. ADK inhibitors and galanin receptor agonists represent a new class of drugs but they may be potentially limited by very poor tolerability. Further insight into their systemic effects of these receptors is needed.

mTOR inhibitors, like Everolimus, represent a clear example of precision-medicine in epilepsy and the first class of potential disease-modifying agents in epilepsy. Everolimus will represent an important therapeutic asset in patients with TSC and data on other developmental brain conditions like focal cortical dysplasias will be of great interest. Data on long term tolerability will be needed as well as risks and benefits in patients with lesional epilepsies that cannot undergo epilepsy surgery.

Ganaxolone, Cannabidavirin, Padsevonil and Selurampanel probably represent the fourth generation of AEDs if they successfully proceed to subsequent stages. Data on general tolerability, effects of cognition and behaviour as well as the potential for interactions in polytherapy will be key element for the success or decline of these drugs.

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