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Review

Mechanism of Anti-seizure Medications and Emerging Trends in Epilepsy Treatment

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Abstract: About one percent of the world's population is affected by epilepsy. Epilepsy-induced psychiatric co-morbidity and mortality impose a huge burden on patients, their families, and society. Anti-seizure medications (ASMs) are drugs used to control seizures in patients with epilepsy. Epilepsy constitutes a spectrum of disorders, with various underlying causes. Hence, finding the right drug to control seizures with minimal side effects is a difficult task for clinicians. Besides controlling seizures, many ASMs have off-target effects that result in unwanted side effects. Compared to first and second-generation drugs, third-generation drugs have shown better tolerance. Even though the target of many ASMs is known, their mechanism of action is not well understood. The main mechanism behind epilepsy is defined as an imbalance in the excitatory-to-inhibitory ratio in neurotransmission. So, the key target of ASMs is the ion channels controlling the intrinsic property of neurons like sodium channels, potassium channels, and calcium channels, the excitatory synaptic transmission via glutamate receptors, and the inhibitory synaptic transmission by GABA receptors. Here we review the role of ion channels in epilepsy, and how the ASMs act on them for seizure control.

Keywords: Anti-seizure medications; antiepileptic drugs; ion channels; epilepsy; pharmacogenetics; gene therapy; drug target

1. Introduction

Epilepsy is the most common brain disorder which affects 70 million people all over the world [1]. It constitutes a spectrum of disorders similar to autism spectrum disorders. Epilepsy is caused by multiple factors: febrile seizures, brain tumors, genetic mutations of ion channels, brain infections and injuries, metabolic disorders, and neurodegenerative diseases. The real mechanism of epileptogenesis that leads to epilepsy is still unknown. The change in excitatory to inhibitory ratio is regarded as the main mechanism of epilepsy. Epileptic seizures are the product of hyper-synchronization of neuronal activity in the brain. The uncontrolled seizures cause neuronal cell death in the hippocampus; it also induces neuronal sprouting (mossy fiber spouting), which causes changes in the structure and function of neuronal circuits in the brain. Moreover, in epilepsy models and patient samples, a change in the expression of various ion channels in the neuronal membrane has been observed [2-5]. The change in neuronal circuit architecture impairs the original functions of the brain areas and contributes to seizures and comorbidities, including impaired learning and memory, mood disorders, and defects in cognitive functions. Moreover, to control seizure activity, the ASMs target ion channels and synaptic transmission. Thus, ASMs may also interfere with the normal brain functions and will add to the impairments. The correct diagnosis and treatment with appropriate ASM are the mainstay of treatment. The duration of seizures usually varies from short-termed to prolonged distress (more than 5 minutes) [6]. The seizures itself and/or ASMs can lead to cognitive impairments [7]. Treatment for epileptic

seizures has vastly improved; originally starting from bromide to the currently available 28 ASMs. This extended choice of ASMs has allowed physicians to select the most suitable drug based on a patient's unique profile. However, despite having many choices, we still are only able to treat the symptoms and not the underlying cause of epileptogenesis and epilepsy. Also, 30% of patients with epilepsy show resistance to ASMs. So, understanding the basic mechanism of epilepsy and mechanism of action of ASMs will help us to bring better drugs to treat patients with epilepsy. Treatment of epileptic patients with ASMs sometimes makes the conditions worse because of lack of knowledge about the complete mechanism of action of the drugs and their unforeseen side effects [8]. In addition, ASMs exert side effects by interfering with the mechanisms of memory formation and cognitive functions. In this review, we mainly discuss the role of ion channels and receptors in epilepsy, the mechanism of action of ASMs, and new developments in this field of research.

2. Role of Ion Channels in Epilepsy

Endogenous chemicals, called neurotransmitters, transfer information across synapses and regulate excitatory and inhibitory neurotransmission by binding to specific ion channels and receptors (Figure 1). Seizures are caused by an imbalance in the excitatory to inhibitory ratio in neuronal circuitry [5,9,10]. The main ion channels involved in epilepsy are the glutamate receptors, GABA receptors, sodium channels, potassium channels, and calcium channels.

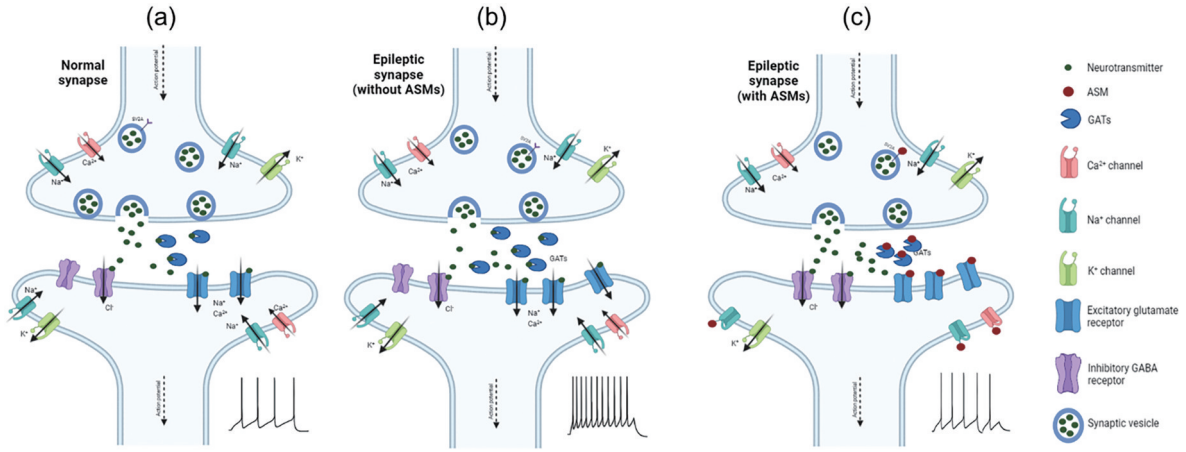

Figure 1. Synaptic transmission in normal and epileptic neuronal synapses. Synaptic transmission in the normal synapse is shown **(a)**. In epileptic synapses, there is an increase in the number of action potentials compared to normal synapse **(b)**. In epileptic synapse, ASMs act on the targets and reduce the number of action potentials **(c)**. Permeability of different ion channels in presynaptic and postsynaptic membrane is also shown. The targets of ASMs to these channels are shown in the epileptic synapse.

2.1. Glutamate Receptors

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system (CNS) [11]. There are four types of ionotropic glutamate receptors, namely alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPAR), kainate receptors (KAR), *N*-methyl-D-aspartate receptors (NMDAR), and metabotropic glutamate receptors (mGluR). The ligand-binding ion channel has a neurotransmitter-binding site and a pore that acts as a channel to transport ions across the membrane. Glutamate receptors are permeable to sodium, potassium, and calcium ions. The calcium permeability is determined by the subtypes [12]. mGluRs are metabotropic receptors with extracellular domains, which act as a binding site for neurotransmitters. The binding of neurotransmitters activates the G-protein which then leaves the receptor and binds to the effector protein [13]. The ligand-gated receptors are responsible for the fast synaptic transmissions and the metabotropic receptors are responsible for the slow synaptic transmission. The kainic acid model of epilepsy is a well-studied animal model in epilepsy research [14]. Autoimmune antibodies against glutamate receptors were found in a sub-population of patients with epilepsy [15]. Previous studies have explored the role of NMDA receptor subtypes in epilepsy models [5,16,17]. Clinical studies have also

shown that an increase in NMDA receptor activity leads to hyperexcitability of pyramidal neurons in patients with mesial temporal lobe epilepsy (MTLE) [18].

2.2. GABA Receptors

GABA is a neurotransmitter that controls the inhibitory neurotransmission in the brain. GABA binds to two types of receptors, $GABA_A$ and $GABA_B$ receptors. $GABA_A$ receptors are responsible for fast inhibitory neurotransmission. These receptors provide major inhibitory currents in the brain. GABA acts as an excitatory neurotransmitter during developmental and prenatal stages. This is primarily mediated by the regulated expression of NKCC1 and KCC2 chloride importer and exporter respectively [19]. In the early stages of development, there is upregulation of NKCC1 transporter which increases the intracellular Cl^- concentration and facilitates GABA-mediated excitatory action [20]. $GABA_A$ receptors can be present at both synaptic and extra-synaptic regions of the neuron. Synaptic receptors produce phasic currents whereas extra-synaptic receptors are responsible for tonic currents caused by extracellular GABA. $GABA_B$ receptors are G protein-coupled receptors that provide slow and prolonged inhibition by activating the inwardly rectifying K^+ channels or by inhibiting voltage gated Ca^{2+} channels [21]. Pentylenetetrazol (PTZ), a $GABA_A$ receptor antagonist, has been extensively used to model epileptic seizures in rodents [22] and zebrafish [23]. Benzodiazepines, which act as modulators by increasing the binding affinity of GABA to its receptor, have been extensively used as anticonvulsants. A decrease in synaptic $GABA_A$ receptors was observed in an animal model of *status epilepticus*. The decrease was related to the fast internalization of GABA receptors [24]. Barbiturates are another class of anticonvulsants that increase the open-state time of $GABA_A$ receptors [25]. Antibodies against $GABA_A$ and $GABA_B$ were found in patients with autoimmune epilepsy [15].

2.3. Voltage-gated Sodium Channels

Voltage-gated sodium channels are essential for action potential initiation in excitable cells. The channel is a multimeric complex, composed of α and β subunits. The α subunit (260 kDa) is the main subunit which contains the pore forming region and is necessary for the function of the channel, while β(1 – 4) subunits modulate the kinetics and voltage dependence of sodium channels [26]. The α subunits are coded by 10 genes, namely Nav1.1 – Na_v1.9 and the tenth sodium channel is not voltage gated. Out of these 10 subunits, around seven are expressed in the nervous systems. Nav1.1, Nav1.2, Nav1.3 and Nav1.6 are expressed in the central nervous system and Nav1.7, Nav1.8 and Nav1.9 in the peripheral nervous system [27, 28]. The α subunit of the sodium channel consists of four homologous domains (I – IV), and each of these domains comprises of six transmembrane segments (S1 – S6). The S5-S6 of each domain fold collectively to form a functional central pore. This central pore structure determines the selectivity and conductivity of the channel [29]. β subunit is composed of one N-terminal extracellular domain, one transmembrane domain, and one C-terminal intracellular domain. One or more β subunits can be bound with one α subunit [30]. These subunits have regulatory functions like cell adhesions and they can also modulate the cell surface expression of VGSC, which helps in the regulation of the excitability of the cells [31]. Sodium channel mutations are responsible for many diseases including epilepsy, cardiac arrhythmia, and chronic pain [32].

2.4. Voltage-gated Calcium Channels

Voltage-gated calcium channels are essential membrane proteins, which allow calcium entry to the cells. The role of calcium channels is not only to depolarize the cells but also to initiate intracellular signaling. The opening of the calcium channel and entry of calcium into the cell triggers many processes, including neurotransmitter release, activation of calcium dependent enzymes like CAMKII, protein kinase C and gene transcriptions [33]. The uncontrolled activation of these channels leads to cytotoxicity [34]. The structure of calcium channel is quite homologous to the sodium channel. The channel is made up of the main pore forming subunit, which is either α1 alone or accompanied with the auxiliary subunits β(1–4) and/or α2δ(1–4). The α1 subunit determines the biophysical and pharmacological properties. The auxiliary subunits are involved in trafficking and can modulate the channel properties. Calcium channel α1 is encoded by the gene CACNA1x, which contains 10 isoforms. The Cav1.1–Cav1.4 are known as L-type channels, Cav2.1–Cav2.3 are named as P/Q, N, R type channels respectively and Cav3.1–Cav3.3 are called T type channels. Depending

upon opening voltage, calcium channels are classified into high voltage activated (HVA) or low voltage activated (LVA), respectively [35]. HVA channels include N-, P/Q-, and R-types which are involved in strong depolarization and L-type which regulates synaptic input at the somato-dendritic level. Whereas, the LVA channel can open to slight depolarizations and generates transient (T-type) currents at or below resting membrane potential, which participate in the intrinsic oscillatory activity [35]. The distribution of the channels is different in different areas, Cav1.1 is mainly in skeletal muscles, whereas Cav2 is mainly found in neurons and Cav3 in all excitable cells [36]. Mutations in the calcium channels are related to night blindness, neuropsychiatric disorders, cardiac dysfunction, and pain [37]. The α2δ subunit of calcium channel is the target of gabapentin used in epilepsy treatment.

2.5. Voltage-gated Potassium Channels

Voltage-gated potassium channels are present in the cell membrane of both excitable and non-excitable cells and control the exchange of K^+ across the membrane [38]. Voltage-gated potassium channels play a major role in the regulation of neuronal excitability, resting membrane potential and release of neurotransmitters. It balances between input and output in individual neurons and is responsible for the repolarization phase of the action potential. Depending upon the structure and function, these channels can be classified into three classes: the voltage-gated (Kv) (six transmembrane domains (TMs), tandem pore domain (K2P) (four TMs) channels, and inwardly rectifying (Kir) (two TMs), [39]. Irrespective of the class, all potassium channels are divided into two parts: the pore forming domain through which transport of K^+ takes place and the regulatory domain which responds to various stimuli and ligands. KCNQ2/Q3 are voltage-gated potassium channels abundantly present in the central nervous system (CNS). They are known for controlling neuronal network synchronization and are present in both pre- and post-synaptic neurons [40]. Kv1. x channels are also voltage-gated channels, which are abundantly present on axons and nerve-end peaks of many regions of CNS. Repolarization, release of neurotransmitter, and conduction of impulse are the main roles played by Kv1. x channels [41, 42]. Antibodies against K^+ channels were detected in autoimmune epilepsy patients [43]. In an in-vitro model of epilepsy, perfusion of high potassium is used to induce epileptiform activity in slices, which is widely used to study the mechanism of epilepsy [44,45].

3. Other Factors Contributing to Epilepsy

3.1. Genetic Abnormalities

Advances in genomic techniques, like next-generation sequencing, have helped us to investigate genes involved in epilepsy. Almost half of epilepsies have a genetic background [46]. In total, there are 977 genes associated with epilepsy, out of which, 84 are considered as “epilepsy genes”. 536 out of 977 genes are “epilepsy-related” genes, relating to physical abnormalities and seizures [47]. However, epilepsy associated genes show large heterogeneity. For example, mutations of the four genes which code for four different subunits of calcium channel, can cause similar, but not identical, phenotypes. Each of these mutations causes different seizure types [46].

3.2. Metabolic Disorders

There are various metabolic disorders linked with epilepsy. Metabolic disorders are defined as metabolic abnormalities that manifest in the form of biochemical changes throughout the body. In many cases, metabolic disorders are linked to genetic defects. The area of metabolic epilepsy is expanding as little is known about the mechanisms behind it [48]. The role of the ketogenic diet has been extensively studied in improving the seizure control by increasing the blood aceto-acetate and 3-hydroxybutyrate levels and decreasing alanine levels in the blood. The mechanism by which the ketogenic diet reduces seizure frequency is still unknown.

3.3. Immune Disorders

The detection of autoantibodies has opened a new concept in understanding the etiology of some epilepsies [49]. It was observed that patients with faciobrachial dystonic seizures have high levels of voltage-

gated potassium channel (VGKC) complex antibodies prior to the development of limbic encephalitis [50]. AMPA receptors [51] and $GABA_B$ receptors [52] are the other antibody targets for patients with limbic encephalitis and temporal lobe epilepsy. Autoantibodies for α1, β3, and γ2 subunits are associated with seizures and status epilepticus in the context of autoimmune encephalitis [53-55]. The pathogenic role of immunity has been described based on immune-modulating treatments and inflammation markers in epileptic patients [56]. Epilepsy related to autoimmune encephalitis is increasingly diagnosed, due to the emergence of antibody testing. This includes anti-NMDA receptor encephalitis and anti-LG11 encephalitis [57]. With the emergence of these therapeutic techniques, targeted immunotherapies could be given to patients [48].

3.4. Prenatal Injuries

Prenatal injuries are defined as injuries caused to the fetus before birth. Trauma, X-ray radiation, chorioamnionitis (infection within the womb), metabolic disorders, history of congenital malformations in the family, and adverse events like this occurring during the brain development of gestation period from 6−20 weeks are considered as prenatal injuries which can initiate epileptic seizures [58].

3.5. Environmental Factors

Environmental factors such as stressful life events have been suggested as possible triggers for epileptic seizures. Almost 50% of patients, who have had a severe head injury, develop seizures under stressful conditions [59].

4. Anti-seizure Medications (ASMs)

ASMs are used for the treatment of patients with epileptic seizures. Several factors influence the selection of suitable ASMs. ASMs have distinct modes of action; these include blocking the voltage-gated sodium and calcium channels, activation of voltage-gated potassium channels and GABA receptors, blocking the GABA reuptake in the synaptic cleft, inhibiting glutamate receptors, and regulation of synaptic vesicles release [60] (Figure 1). ASMs are also used for non-epileptic conditions, including chronic neuropathic pain, schizophrenia, migraine, various neuromuscular syndromes (neural modulations). In total, approximately 28 ASMs have been developed. The ASMs are arranged chronologically in table 1 and categorized according to their generation.

Table 1. ASMs according to the generation and year.

1st Generation	2nd Generation	3rd Generation
Early 1900–Bromides	1993–Felbamate	2008–Lacosamide
1912–Phenobarbital	1993–Gabapentin	2008–Rufinamide
1937–Phenytoin	1994–Lamotrigine	2009–Vigabatrin
1954–Primidone	1996–Topiramate	2011–Clobazam
1960–Ethosuximide	1997–Tiagabine	2011–Ezogabine
1968–Diazepam	1999–Levetiracetam	2012–Perampanel
1974–Carbamazepine	2000–Oxoarbazepine	2013–Eslicarbazepine
1975–Clonazepam	2000–Zonisamide	
1978–Valproate	2004–Pregabalin	
1981–Clorazepate		

Currently available ASMs have different targets and modes of action. The main targets are voltage-gated ion channels, and inhibitory and excitatory neurotransmission. For more accurate selection of ASMs, the working mechanism should be known. Each ASM has a mode of action. ASMs act either by decreasing the neuron discharge rate or by preventing the spread of discharge from the focus point.

4.1. Sodium Channel Blockers

Sodium channel blockers have been the main target since the beginning of the development of ASMs. The most effective ASMs, targeting Na^+ channels, are phenytoin, carbamazepine, lamotrigine, oxcarbazepine, rufinamide, lacosamide and eslicarbazepine acetate. These drugs cause a reduction in voltage and frequency-

dependent channel conductance [61]. ASMs bind to the inactivated state of the receptor, which suppresses the repetitive firing of neurons. This blocks the action potential-dependent activation of neurotransmitters and also prevents the propagation of action potential from soma to the dendrites [62]. Different Na^+ channel-blocking ASMs have different efficacies as they also have prominent effects on other voltage-gated ion channels [63]. Secondly, they also differ in binding kinetics, for instance, they bind to channels in different states [64]. Phenytoin, carbamazepine, lambotrigine and oxcarbazepine target fast inactivation state of the Na^+ channel [65,66], whereas lacosamide and eslicarbazepine acetate target slow inactivation state [67,68]. Furthermore, Na^+ channels are present at different sites in the neuron, thus efficacy of ASMs may differ depending on the sites targeted by the ASMs. ASMs like lamotrigine, phenytoin and carbamazepine inhibit glutamate release as it targets the Na^+ channels located on pre-synaptic glutamatergic terminals [69,70].

4.2. Calcium Channel Blockers

Voltage-gated Ca^{2+} channels could be of great importance in the anti-seizure mechanism. N-P/Q type calcium channels may be involved in inhibiting the release of glutamate and other transmitters [71]. Many ASMs have been reported to inhibit Ca^{2+} currents as a secondary target. Phenytoin inhibited the Ca^{2+} current in the mouse spinal cord and neocortical culture [72]. Carbamazepine and barbiturates reduced the Ca^{2+} currents in the neocortex, hippocampus, and dorsal ganglia [73]. Lamotrigine and felbamate inhibited the Ca^{2+} currents in neocortical cells [74]. Even though all these drugs show some effect on Ca^{2+} currents, a significant effect was observed above the therapeutical dosage.

4.3. Potassium Channel Modulators

Voltage-gated potassium channels have a major role in the regulation of neuronal excitability. They are known for controlling neuronal network synchronization and are present on both pre- and post-synaptic neurons [70]. Flupirtine acts on the K^+ channels currents in the neocortex and hippocampus, and regulate the excitability of the neurons [76]. Recent studies have shown the role of various potassium channels, including GIRK2, Kv1.1, K_{ATP}, in the regulation of neuronal excitability and seizure susceptibility [77]. More studies are needed to find out the effects of ASMs on different K^+ channels.

4.4. Inhibitory Neurotransmission Modulators

GABA is the main inhibitory neurotransmitter in the brain, which makes it a potential target for anti-seizure medications. Drugs potentiating $GABA_A$ are generally used as sedatives or anesthetics. Drugs that target GABA receptors have shown anticonvulsant properties [73]. The $GABA_A$ receptor has various binding sites for ligands like benzodiazepines, steroids, anesthetic agents, and convulsant toxins. Benzodiazepines, which act via $GABA_A$ receptors, are widely used to control seizures and treat status epilepticus. Tiagabine is a GABA re-uptake blocker and vigabatrin is a GABA-degrading enzyme blocker; they increase the GABA concentration at the synapse [78] and dampen the seizures. Another drug, felbamate possesses dual mechanism as a positive regulator of the $GABA_A$ receptor and antagonist of NMDA receptors [29]. However, it was discontinued because of reports of aplastic anemia [79] and hepatic failure [80]. Other drugs like ezogabine, eosigamone and stiripentol have a different primary mechanism of action, which also target GABA receptors as a secondary mechanism of action [81]. It was observed that a very low dose of clonazepam, which was neither sedative nor anxiolytic, improved cognitive function and memory in Scn1a+/- mice [82]. Two ASMs have been recently introduced, vigabatrin (VGB) and tiagabine (TGB). VGB inhibits the break down of GABA by inhibiting gamma-aminobutyric acid aminotransferase (GABA-AT), whereas TGB prevents the reuptake of GABA in the presynaptic neurons, which increases the concentration of synaptic GABA [81]. More investigations are needed regarding the subtypes of $GABA_A$ receptors in epilepsy, which may lead to the development of new ASMs with less side effects.

4.5. Excitatory Neurotransmission Blockers

Glutamate is the main excitatory neurotransmitter in the mammalian brain. It binds to glutamate receptors and causes neuronal depolarization and excitation. The calcium selectivity is subtype dependent and

over-activation of NMDA receptors is linked to excitotoxicity and cell death. Metabotropic glutamate receptors are G protein coupled receptors and generally act as an auto-receptor on glutamatergic terminals and restrict the release of glutamate. MK-801, which is a non-competitive NMDA receptor antagonist, has also been proven to have antiepileptic effects in the animal model [83]. Perampanel is the only ASM that has selective effects on AMPA-type glutamate receptors [84]. More research is needed to find out the subtypes contributing to epilepsy, to explore better targets and to minimize side effects.

5. Pharmacogenetic Changes Affect ASMs Metabolism

Drug treatment of epilepsy is often associated with unpredictability of efficacy, optimum dose, and adverse effects. These variabilities are suggestively linked to variations in the genetic constitution of patients. Individual patients with a similar epilepsy syndrome, who are taking similar medication, can have a wide range of responses; it may be beneficial to some and adverse to others. This is an indication that individuals possess unique genetic profiles [85]. Genes involved in the transport and metabolism of drugs, and the drug target itself contribute to the variability in the efficacy of ASMs [86]. Pharmacogenetics play a key role in drug response as it relates the drug response with genetic variations. Whole exome sequencing (WES) is an effective method to identify a causative mutant gene in a particular disorder [87]. A recent WES analysis in a Chinese cohort of infants and children with epilepsy identified 81 genes, and 67 patients had multiple phenotypes. These genes, *MMUT, KMT2A, MECP2, HIVEP2, TSCE, KCNQ2, POLG2, SYNGAP1, DGUOK, GALC, ARX, ADNP, COL3A1,* and *SCN2A,* were implicated in most cases of epilepsy [88]. An Italian study identified p. Asp252Asn mutation in *TMEM106B* by WES in a 20 months infant [89]. *TMEM106B* is implicated in the acidification of late endosome-lysosome morphology. It is a suggested candidate gene for screening in infants with epilepsy. Personalized pharmacogenetics may impact the drug dose response. For example, a mother was able to achieve seizure-control using monotherapy; however her son inherited her mutation in *DEPDC5* and did not respond to multiple anti-seizure drugs [90]. This may be due to the individual variation in the genetic constitution. Seizure outcome changes depending on the type of mutations in ion channels. For example, missense mutations in sodium channels (SCN2A) elicit early onset (<3 months) infantile epilepsy, whereas truncating, splice-junction, and nonsense mutations result in late onset epilepsy or no epilepsy. In a cohort of early onset epilepsy, many patients responded to phenytoin but not to phenobarbital and levetiracetam [91]. The striking effect of lidocaine (prototypic sodium channel blocker) in Ohtahara syndrome (early onset) was reported in a patient with *SCN2A* mutation [92]. Thus, genomics and bioinformatics analyses of individual genotypes could predict the effectiveness of a re-purposed drug or indicate the need for inventing a new drug. This will significantly help the decision-making process in the clinics, and has wide implications for therapy outcome and health of the patients. Furthermore, it could also reduce exorbitant healthcare costs.

There are physiological changes in hormone levels from infancy to childhood, adolescence, and adulthood. During these periods, the capacity of the hepatic and renal systems to metabolize drugs drastically changes. It could impact the pharmacokinetics of ASM in the body [93, 94]. In pregnancy, the body also undergoes marked physiological changes. During pregnancy, metabolite binds to the protein and their distribution and absorption are decreased, and the excretion of metabolites is also increased. Moreover, in the pregnancy period, the activity of P450 (CYP) and uridine glucuronyl transferase (UGT) are increased. Hence, during pregnancy, the concentration of ASM fluctuates in serum [95]. Another challenge with ASMs is polypharmacy leading to drug-drug interactions [96].

The polymorphisms in metabolizing liver enzymes, including CYP2C9, CYP2C19, and CYP4CA, affect the efficacy of ASMs [97]. Phenytoin is metabolized by CYP2C9 and CYP2C19. Mutations in these enzymes adversely affect the efficacy of the drug [98, 99]. In addition to CYP, valproic acid metabolism requires the activity of UGT, thus mutations in these enzymes would compromise valproic acid clearance [100]. Mutations in P-glycoprotein, a drug efflux transporter, is known to cause resistance to ASM [101]. The specific mutation in a drug target, like a sodium channel SCN1A, could modulate the dose effect [102]. However, many polymorphisms in sodium channels are refractory to dose effect [103]. Though many mutations are known to affect the efficacy of ASMs, genetic tests have yet to be developed because we lack a comprehensive understanding of the pharmacogenetics [104].

The advances in Next Generation Sequencing and in silico bioinformatics can help solve this challenge. This is especially true when analyzing the mutations in transporters and solute carriers [105].

6. Adverse Effects of ASMs

WHO defines an adverse drug effect as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [106]. Every medication has adverse effects with varying severity. ASMs also have been associated with different side effects, including impairment in learning and memory, psychiatric comorbidities, dizziness, and ASM toxicity (Figure 2). Adverse effects in terms of tolerability vary from patient to patient as it depends upon several factors, including the genetic makeup of the patient and how rapidly the dose is escalated [107].

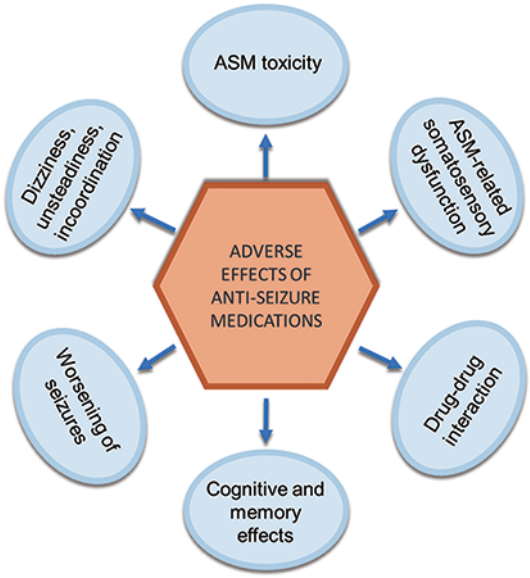

Figure 2. The schematic diagram summarizes the adverse effects of ASMs in patients with epilepsy. Ion channels determine the intrinsic and synaptic properties of neurons. Since ion channels are the main targets of ASMs, it also effects the normal physiological functions and causes side effects like delay in somatosensory effects, impaired learning and memory and cognitive functions. ASMs toxicity is caused due to the dosage and drug-drug interactions.

The adverse effects may be acute, chronic or related to serum concentration. Phenytoin concentration causes movement disorders, bone disorders and skin rashes. The drugs also have effects on pregnant women; for instance, valproate is contraindicated for women with idiopathic generalized epilepsy. Use of other ASMs during pregnancy can lead to minor and major fetal anomalies, affect mental development and lead to maternal seizure disorders [108]. The site of action and adverse effects of ASMs has been summarized below (Table 2).

6.1. Neuropsychological Effects of ASMs

ASMs are also associated with neuropsychological effects. Even minor effects can have clinical significance and have an impact on the patient's quality of life. Patients with epilepsy mostly suffer from cognitive and memory impairment [124,125]. The effect of ASMs on cognitive and memory impairment is well-established [126,127]. Tolerability, rather than efficacy is the major deciding factor when prescribing ASMs to patients with epilepsy. In two separate comparative studies conducted [128,129], including phenytoin, carbamazepine, phenobarbital, and primidone, all the ASMs were linked with cognitive impairment. The ASM, primidone, had a more negative impact on patients' cognition, while phenytoin and carbamazepine had less. However, all of these drugs were seen to have an impact on patients' cognition. Phenytoin is a first-line drug, and is given to suppress acute seizures because it can be given intravenously

Table 2. ASMs with their primary site of action and commonly observed adverse effects.

Drug	Site of Action	Adverse Effects	Reference
Phenytoin	Na+ channel	Cause movement disorders, hypocalcemia, megaloblastic anemia, liver dysfunction, skin rashes, affects immune system.	[109]
Valproic acid	Na + channel and GABA release	Personality change, thrombocytopenia, liver dysfunction, hair loss	[110]
Carbamazepine	Na+ channel	Ataxia, movement disorders, aplastic anemia, skin rashes, increased production of ADH hormone	[111]
Clonazepam	GABAergic transmission	Drowsiness, ataxia and behavioral changes	[112]
Oxcarbazepine	Na+ channel	Dizziness, nausea, fatigue and rarely Stevens–Johnson syndrome	[113]
Phenobarbital	GABAergic transmission	Intellectual impairment, aplastic anemia, hepatotoxic effects.	[109]
Ethosuximide	Ca^{2+} channel	Movement disorders, leucopenia, systemic lupus erythematous	[114]
Zonisamide	Ca^{2+} channel	Dizziness, anorexia, Fatigue, headache, mental slowing	[115]
Topiramate	Na + channel	Induce fatigue and drowsiness	[110]
Lacosamide	Na + channel	Dizziness, headache, drowsiness, diplopia, and cardiovascular abnormalities.	[116]
Felbamate	GABA A and NMDA receptor	Vomiting, headache, insomnia, aplastic anemia and serious liver damage	[117]
Primidone	Na + channel	Drowsiness, anorexia, dysarthria, unsteadiness and headaches	[118]
Lamotrigine	Na + channel	Ataxia, skin rash, headache, insomnia, and nausea	[119]
Tiagabine	GABAergic transmission	Dizziness, asthenia, somnolence, tremor, confusion and depressed mood	[120]
Rufinamide	Na+ channel	Somnolence, weight loss and status epilepticus	[121]
Vigabatrin	GABAergic transmission	Excitation, agitation, insomnia fatigue, somnolence	[122]
Perampanel	AMPA receptor	Dizziness, Psychiatric and behavioral changes	[84]
Eslicarbazepine acetate	Na+ channel	Headache, somnolence, dizziness, and paresthesia circumoral lips or tongue	[123]

and has a faster effect. However, it is also associated with cognitive difficulties in patients with epilepsy [130, 131]. In a previous study, it was observed that when patients, with mild seizure attacks and low cognitive problems, were treated with ASMs, including phenytoin or carbamazepine, they performed worse in various neuropsychological tests and tasks [132]. In another comparative study, between oxcarbazepine and phenytoin, it was seen that both had a significant reduction in the cognitive functions of patients with epilepsy [133]. When cognitive and behavioral function were tested in epileptic patients undergoing conventional treatment (CBZ and VPA), it was observed that there was an increased risk of cognitive dysfunction. Areas of cognitive function that were affected include total verbal reasoning, the memory of subjects, bead memory, nonverbal short-term memory, and behavioral and psychiatric symptoms, such as, depression aggression and neurosis [134]. Dravet syndrome which is caused by a heterozygous loss-of-function mutation of SCNA1 gene, which encodes for α subunit of Na^+ channel $Na_v1.1$, is also associated with neuropsychiatric comorbidities, including autistic-like behavior, cognitive impairment and social interaction deficit, which overlap with the use of ASMs [135]. The reason behind these effects is attributed to the fact that ASMs not only reduce neuronal firing but also may impair neurotransmitter release, neuronal excitability, and factors critical for information processing and learning [136,137]. It was also observed that sometimes patients treated with ASMs demonstrate worse scores for memory compared to untreated patients [137].

6.2. Synaptic Plasticity

The role of synaptic plasticity in learning and memory and other cognitive functions are well recognized [138]. Studies have suggested that the progression of epileptic stages may overlap with the mechanism underlying long term plasticity (LTP & LTD), and may impair learning and memory [139,140]. The reason behind cognitive impairment in epilepsy is still not clear. It may be the epilepsy itself and/or ASM can cause cognitive impairments. Previous studies have reported sodium valproate, commonly used ASM impairs LTP and LTD [141]. In an animal study, [142] compared the effects of different ASMs in LTP in mouse brain slices. They reported a reduced LTP by carbamazepine and phenytoin, whereas lamotrigine did not affect the LTP. Levetiracetam treatment improved the synaptic transmission in the chronic epilepsy model, but it did not change the slope of LTP in epileptic mice compared to controls [143]. [144] studied the effect of carbamazepine, oxcarbazepine, and eslicarbazepine and found carbamazepine and oxcarbazepine increased the synaptic excitatory currents at a lower valid therapeutical concentration, but this effect was not caused by eslicarbazepine [144]. In another study, treating epileptic rats using brivaracetam was able to partially reverse the LTP to control levels [145]. In a clinical study, [146] found that LTP like cortical plasticity was reduced in subjects who took an oral dose of levetiracetam, whereas diazepam, lamotritrigine, tiagabine, and piracetam showed no significant effect in LTP like plasticity [146]. More studies are needed to understand the action of ASMs in synaptic transmission and plasticity.

7. New Emerging Drug Targets

Currently used ASMs majorly target voltage-gated ion channels, and GABA and glutamate receptors. Mostly, the usage of these drugs was based on their anti-seizure efficacy without completely understanding the mechanism of action. The progress made in understanding the mechanism behind epileptogenesis helped us to develop a target-based drug discovery approach for better efficacy and fewer side effects [86]. Recently, the use of rapamycin in the treatment of epilepsy in patients with tuberous sclerosis is being validated. Rapamycin attenuates mTOR dysregulation which is the major cause behind seizures in patients with tuberous sclerosis [147,148]. In another study using hippocampal slices from patients with TLE, depolarizing activity of $GABA_A$ transmission was observed; this was due to the increased expression of NKCC1 transporter, which changes the intracellular concentration of chloride ion. Blocking of NKCC1 transporter by bumetanide (NKCC1 inhibitor) inhibited the seizures in neonates in the rat model of epilepsy [149]. Clinical trials are ongoing to evaluate the efficacy of bumetanide in children with neonatal seizures [150]. There is increasing evidence of inflammatory mediators in the brain, which are involved in the initiation of seizures and epileptogenesis [151,152]. Interleukin-1β (IL-1β) produced by glial endothelial cells in the blood brain barrier contributes to neuronal injury and hyperexcitability of neurons in epileptogenesis. It was observed that IL-1β receptor antagonist, anakinra, used in the treatment of rheumatoid arthritis reduced seizures associated with blood brain barrier breakdown in animal models [153,154]. Further understanding of the cellular mechanism behind seizures and epilepsy will allow us to target new areas to reduce the seizures and cure the underlying pathophysiology of epilepsy.

8. Gene Therapy

Gene therapy is emerging as a new strategy to treat patients with epilepsy. It might be a better treatment for patients with gene mutations and drug resistance, where conventional therapies have failed to control seizures. In preclinical trials, gene therapy has been effective in controlling seizures in animal models of epilepsy [155] . Viral vector has been the choice of approach due to their high efficiency when delivering the interest gene and it is also target specific. Commonly used viral vectors for the brain are adeno-associated virus (AAV), lenti virus (LV) and herpes simplex virus (HSV). All of these viruses have their own advantages and disadvantages [156-158]. In Dravet syndrome (DS) mouse model, where GABAergic neurons show reduced expression of sodium channel Nav1.1α subunits, overexpression of auxiliary subunit Navβ1, using AAV, increased the Nav1.1α subunit expression in the cell and increased the survival rates of the mice. Thus neonatal treatment with Navβ1-AAV in a mouse model of DS is promising and opens new avenues for the treatment of DS [159]. In another study, immediate early gene promotor was used to target the hyperactive neurons in a model of epilepsy. Here the authors engineered the expression of the Kv1.1 in a cell-autonomous

manner in the hyperactive neurons, which reduced the cell excitability and produced an antiseizure effect [160]. Interestingly, the cell-autonomous treatment did not affect physiological behavior. This novel technique has wide implications for the treatment of neuronal disorders. Patients suffering from epilepsy with a genetic origin have multiple genes involved and which affect a larger region of the brain [161]. This requires widespread gene transfer, but with current developments in this field, we can only use gene therapy to provide a localized effect. New developments in non-viral vectors and new gene editing tools (CRISPR-Cas) will bring changes in this field.

9. Conclusions

Significant and continuous advancements are happening in the field of epilepsy treatment. In the last three decades, many ASMs have been discovered and licensed. However, the main drawback of these ASMs is the unwanted behavioral and cognitive side effects, and drug resistance in patients with epilepsy. Better understanding of the cellular mechanism of action of ASMs and drug resistance is required. Gene therapy is another option for epilepsy treatment, which is a slowly progressing area. Furthermore, ion channel subtypes involved in epilepsy need to be characterized, which may help the development of drugs with better targets and less side effects.

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