Received: 17 May 2021 | Revised: 1 July 2021 | Accepted: 6 July 2021

DOI: 10.1002/npr2.12196

REVIEW ARTICLE

NEUROPSYCHOPHARMACOLOGY REPORTS

WILEY

Neuropharmacology of Antiseizure Drugs

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Funding information
The author received no financial support for the research, authorship, and/or publication of this article

Abstract

Background: Antiseizure drugs (ASDs) are the primary therapy for epilepsy, with more than 20 drugs introduced into clinical practice to date. These drugs are typically grouped by their mechanisms of action and therapeutic spectrum. This article aims to educate non-neurologists and medical students about the new frontiers in the pharmacology of ASDs and presents the current state of the literature on the efficacy and tolerability of these agents.

Methods: Randomized controlled trials, observational studies, and evidence-based meta-analyses of ASD efficacy and tolerability as initial monotherapy for epileptic seizures and syndromes were identified in PubMed, EMBASE, the Cochrane Library, and Elsevier Clinical Pharmacology.

Results: The choice of ASD varies primarily according to the seizure type. Practical guidelines for ASD selection in patients with new-onset and drug-resistant epilepsy were recently published. The guidelines have shown that the newer-generation drugs, which have unique mechanistic and pharmacokinetic properties, are better tolerated but have similar efficacy compared with the older drugs. Several ASDs are effective as first-line monotherapy in focal seizures, including lamotrigine, carbamazepine, phenytoin, levetiracetam, and zonisamide. Valproate remains the first-line drug for many patients with generalized and unclassified epilepsies. However, valproate should be avoided, if possible, in women of childbearing potential because of teratogenicity. Toxicity profile precludes several drugs from use as first-line treatment, for example, vigabatrin, felbamate, and rufinamide.

Conclusions: Antiseizure drugs have different pharmacologic profiles that should be considered when selecting and prescribing these agents for epilepsy. These include pharmacokinetic properties, propensity for drug-drug interactions, and adverse effects.

KEYWORDS

antiseizure drug, epilepsy, seizure types

1 | INTRODUCTION

Epilepsy is a chronic disorder of brain function characterized by recurrent seizures.[1] At any one time, about 1% of the population requires medication to treat epilepsy.[2] The antiseizure drug (ASD) is the mainstay of treatment. The choice of ASDs varies with different seizure types and epileptic syndromes.[3] The appropriately chosen ASD provides adequate seizure control in 60%–70% of patients.[4] There is no general agreement on when treatment should start after a "first seizure," but randomized controlled trials (RCTs) in adult and pediatric patients have shown that early treatment reduces the recurrence for at least two years from the first seizure.[5] The ASDs are often administered orally for a long period of time to prevent seizure recurrence. In designing a therapeutic approach, the use of a single drug (monotherapy) is preferred because of fewer adverse effects. However, 30% of the patients will continue to have uncontrolled seizures and multiple drugs are often used simultaneously.[6] Monotherapy trials of two ASDs that are appropriate first-line treatment for the patient's seizure type usually be initiated before combinations are tried. Patients who do not achieve seizure control following adequate trials with two or more appropriate drugs are considered drug-resistant.[6] The International League Against Epilepsy (ILAE), in 2010, has proposed the definition of drug-resistant epilepsy (often used interchangeably with "'medically refractory"' and "'intractable") as "failure of adequate trials of two tolerated, appropriately chosen and used antiseizure drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[7]

The older-generation ASDs were introduced into clinical practice more than four decades ago. Research has shown that 30%–40% of people treated with an older ASD as monotherapy (including carbamazepine and valproate) experience adverse effects that contribute to treatment failure.[8] This spurred a continuing search for new ASDs with novel molecular targets that could provide optimal care for patients with epilepsy.[9,10] The past three decades have seen the licensing of about 20 newer- (second- and third-) generation ASDs with unique mechanisms of action and pharmacokinetics following a period of relative paucity.[11] This advent has expanded the epilepsy therapeutic armamentarium and allowed the drugs to match the individual patient's characteristics. The American Academy of Neurology (AAN) subcommittee reports in 2004 observed that newer ASDs were not different in controlling seizures but have better tolerability, particularly fewer neurotoxic adverse effects.[12,13] In 2017, the ILAE published a new classification for seizure types and epilepsy syndrome to improve our understanding of epilepsy and include missing seizure types.[14-17] This classification replaced the previous versions published in 1981[18] and 1989,[19] and extended in 2010,[20] and has been of paramount importance to accurately classify the patient's seizure type(s). In 2018, the AAN and American Epilepsy Society (AES) subcommittee published updated guidelines for ASD selection in adult and pediatric patients with new-onset and treatment-resistant epilepsy.[21,22] However, the guidelines primarily relied on studies that compare the first- and second-generation ASDs and found limited data for third-generation drugs. Given the rapid advance in the development of ASDs in recent years and the continuous updates in definitions, classifications and treatment guidelines for seizure types, and epilepsy syndromes, this article aims to provide non-neurologists and medical students with a complete overview of the new frontiers in the neuropharmacology of antiseizure drugs. The ASDs classification, pharmacokinetics, mechanisms of action, clinical use, and adverse effects are reviewed herein based on a comprehensive assessment of the current literature and recently published US and UK treatment guidelines.

1.1 | Definition and epidemiology of epilepsy

Epilepsy is "a neurological disorder that is characterized by an enduring predisposition to generate epileptic seizures and the associated cognitive, psychological, and social consequences".[1] Epilepsy is the third most common neurologic disorder; almost 10% of people will experience a seizure during their lives.[2] The prevalence of epilepsy is 6.4 cases per 1,000 persons, and the annual incidence is 67.8/100,000 person-years.[23]

1.2 | Classification of seizure types and epilepsy syndromes

The ILAE classification framework, which was revised in 2017, is the key tool for the diagnosis of individuals presenting with seizures.[14-17] According to that classification, epileptic seizures are classified into "focal," "generalized," and "unknown" seizures, while epilepsy is classified into "focal," "generalized," "combined generalized and focal," and "unknown" epilepsy. Focal-onset seizures can be further described as focal aware (previously called simple partial), impaired awareness (complex partial), or focal to bilateral (secondarily generalized) tonic-clonic seizures. Generalized seizures are classified into generalized tonic-clonic (formerly idiopathic) seizures, motor (myoclonic and other motor) seizures, and nonmotor (absence) seizures. Etiologies of seizures and epilepsy syndromes have been reintroduced in the 2017 ILAE classification of seizure types and epilepsy syndromes, to include "genetic," "structural," "metabolic," "infectious," "immune," and "unknown." For a detailed description of seizure types epilepsy syndromes, see the ILAE Web site.[24]

1.3 | Drug treatment of epilepsy

Epilepsy can persist for years and often for the patient's lifetime. ASDs are the primary therapy for epilepsy and are symptomatic treatments that control seizures.[3] The choice of ASDs varies with different seizure types and epileptic syndromes.[3] ASDs have many different pharmacologic profiles that are relevant when selecting

and prescribing these agents in patients with epilepsy. This includes pharmacokinetic properties, propensity for drug-drug interactions, and adverse-effect profiles and toxicities. All older-generation ASDs have acute dose-related effects, primarily neurological effects.[25,26] This led to treatment failure in 30%–40% of people with epilepsy receiving an older drug as monotherapy.[8] Hence, there has been a great deal of research into formulating better ASDs, primarily spurred by the fact that the older-generation ASDs do not provide optimal safety, tolerability or seizure control for many patients with epilepsy. Over the past three decades, 20 newer-generation ASDs have been approved for clinical use,[11] and it was hoped that these drugs would have better efficacy in controlling seizures than older-generation drugs. However, the AAN subcommittee reports in 2004 and 2018 observed that the newer-generation ASDs were "not different" in controlling seizures, but better tolerated than the older drugs.[12,13,21,22]

1.4 | Classifications of ASDs

ASDs are classified as older (first-) generation or newer (second- and third-) generation agents. The older-generation ASDs introduced into clinical practice more than four decades ago include phenobarbital, phenytoin, primidone, ethosuximide, valproate, carbamazepine, clonazepam, and clobazam. The "second-generation" ASDs, which have been approved for the treatment of epilepsy since the late 1980s, include, in chronological order, vigabatrin, oxcarbazepine, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, levetiracetam, and zonisamide. The third-generation ASDs include, pregabalin, fosphenytoin, lacosamide, rufinamide, eslicarbazepine, retigabine (also known as ezogabine), perampanel, brivaracetam, cannabidiol, stiripentol, cenobamate, and fenfluramine.[11,12,27,28] The newer ASDs differ substantially in their mechanisms of action, spectra of activity, pharmacokinetics, and adverse effects profiles. Figure 1 presents the classification and year of introduction of ASDs available now. Current information on the other drugs in the pipeline can be found on the Epilepsy Foundation Web site.[29]

1.5 | Pharmacokinetics and drug interactions of ASDs

ASDs are commonly used for long periods of time, and consideration of their pharmacokinetic properties is essential for avoiding toxicity and drug interactions.[30] An ideal ASD should demonstrate complete absorption, linear kinetics, a long elimination half-life, and allowing once or twice-daily dosing. Other favorable properties include low protein binding, lack of active metabolites, and clearance by kidneys. Generally, all ASDs are well absorbed after oral administration, have good bioavailability, and readily cross the blood-brain barrier. Many ASDs are medium to long-acting drugs (have half-lives of >12 hours) and can be administered twice or three times a day. Phenobarbital, phenytoin, zonisamide, eslicarbazepine, and perampanel can often be administered once daily. Extended-release preparations of drugs that have short half-lives (eg, carbamazepine, valproate, levetiracetam, and lamotrigine) may decrease the incidence of adverse effects and allow once-daily dosing. For optimum therapy, therapeutic drug concentration should be monitored in individual patients for some drugs. Examples include carbamazepine, phenytoin, and valproate. Drug levels can be helpful (1) to guide dose adjustments, (2) when breakthrough seizures occur, (3) when an interacting medication is added, (4) during pregnancy, (5) to assess compliance, and (6) to determine whether adverse effects are related to drug levels. Clinically relevant pharmacokinetic profiles of ASDs are summarized in Table 1.

In general, the ASD should be started at a low dose, with increments over several weeks to establish an effective and tolerable regimen. Some agents do not require titration, such as gabapentin and levetiracetam. Clinicians should be aware of certain factors that affect dosing. These factors include nonlinear relationships between dose and drug exposure (eg, phenytoin) and the influence of hepatic or renal impairment on clearance. Metabolism of phenytoin is nonlinear; elimination kinetics shift from first order at a low dose to zero-order at moderate to high dose. As a subsequent, any small increases in the dose may increase phenytoin half-life and serum concentration, and a patient may quickly develop toxicity. A common clinical error is to increase the dosage directly from 300 mg/d

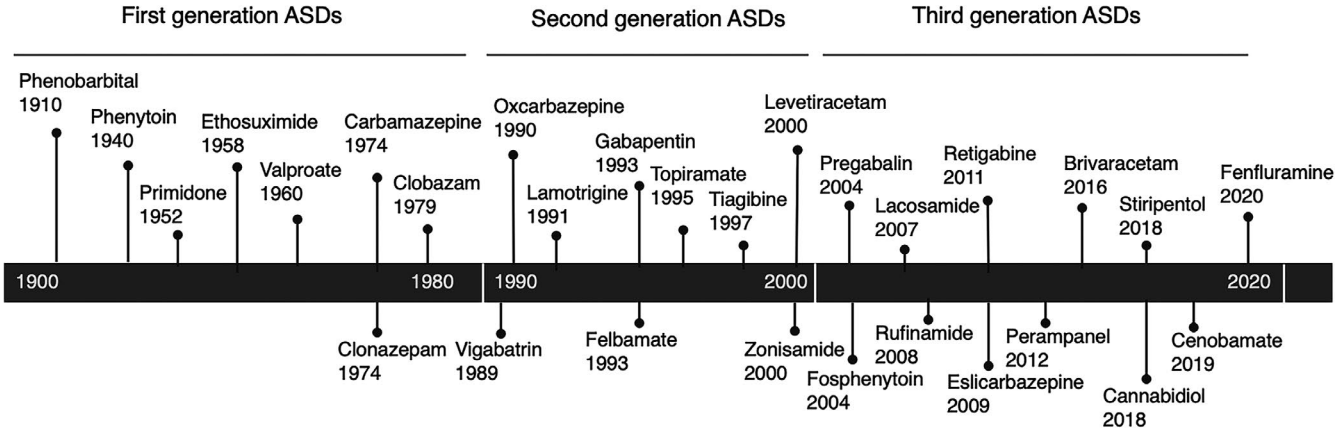

FIGURE 1 Classification and year of introduction of antiseizure drugs

to 400 mg/d; toxicity frequently occurs at a variable time thereafter. Hepatic biotransformation of valproate may lead to hepatotoxicity. Hence, the liver function test is recommended in individual patients.

Most ASDs are metabolized by hepatic enzymes. Carbamazepine, oxcarbazepine, eslicarbazepine, phenobarbital, phenytoin, and primidone are inducers of hepatic cytochrome P450 enzyme and may decrease the effects of other drugs administered concomitantly (eg, valproate). Valproate and clobazam are inhibitors of hepatic enzymes and most likely to elevate the plasma concentration of other drugs administered concomitantly (eg, carbamazepine, ethosuximide, phenytoin, phenobarbital, and lamotrigine). Drug-drug interactions with ASDs are complex since the drugs are often used in combination. These interactions may lead to either inadequate seizure control or drug toxicity. Of the newer drugs, levetiracetam, gabapentin, pregabalin, and vigabatrin are unique. These drugs are eliminated unchanged by the kidney and have no drug-drug interactions. Lamotrigine, perampanel, tiagabine, topiramate, and zonisamide undergo hepatic drug metabolism and have potential drug interactions. Oxcarbazepine, felbamate, and topiramate selectively induce the hepatic metabolism of the oral contraceptive pill, failing birth control.

1.6 | Mechanisms of actions of ASDs

A propensity for seizure generation occurs when there is an imbalance favoring excitation of neurons over inhibition. ASDs actions can generally be viewed in the context of inhibition of excitation or strengthening of inhibition, or both. Inhibition of excitation can be produced by effects on intrinsic excitability mechanisms in excitatory neurons (eg, inhibition of sodium and calcium channel), or on excitatory synaptic transmission (eg, glutamate AMPA and NMDA receptors and synaptic vesicle protein 2A). Enhancement of inhibition is produced by the increased availability of γ-aminobutyric acid (GABA), increased activation of $GABA_A$ receptors, the mediators of inhibition in cortical areas relevant to seizures, and modulation of voltage-gated potassium channel of the Kv7. For some drugs, the precise mechanism of action is not known (eg, valproate, zonisamide, and rufinamide), and some have multiple targets (eg, topiramate and felbamate).[31] The ASD mechanisms of action are summarized in Table 2 and discussed in detail in the remainder sections.

1.7 | Voltage-gated sodium channels blockade

At therapeutic concentrations, carbamazepine, cenobamate, lacosamide, lamotrigine, phenytoin, and zonisamide block voltage-gated sodium channel in neuronal membranes. These agents act mainly on action potential firing and do not directly alter excitatory or inhibitory synaptic responses. However, the effect on action potentials translates into reduced transmitter output at synapses. Topiramate may also act, in part, by this mechanism. Phenobarbital and valproate may act on the sodium channel at high doses. This action is rate-dependent (ie, the block increases with increased frequency of neuronal discharge).[31]

1.8 | GABA-related targets

Benzodiazepines interact with specific receptors ($GABA_A$ receptors) and increase the frequency of GABA-mediated chloride ion channel opening (facilitate inhibitory effects of GABA). Phenobarbital and other barbiturates increase the duration of GABA-mediated chloride ion channel opening. Vigabatrin, an analog of GABA, irreversibly inactivates GABA transaminase, the enzyme responsible for the termination of action of GABA. Valproate also can inhibit GABA transaminase at high doses. Tiagabine selectively inhibits the GAT-1 GABA transporter, causing prolongation of GABA-mediated inhibitory synaptic responses. Gabapentin and pregabalin are structural analogs of GABA but do not act through effects on any mechanism related to GABA-mediated neurotransmission. Instead, the drugs bind to the α2δ subunit of the voltage-gated calcium channel and decrease glutamate release at excitatory synapses. Other drugs that may facilitate the inhibitory actions of GABA include felbamate and topiramate.[31]

1.9 | Calcium channel blockade

Ethosuximide inhibits low voltage-gated T type calcium channels in thalamocortical neurons. Valproate may exert similar action. Gabapentin and pregabalin bind to the $\alpha_{2\delta}$ subunit of voltage-gated calcium channel and may decrease glutamate release at excitatory synapses (the precise mechanism is not known).[31]

1.10 | Glutamate synapses and other mechanisms

Levetiracetam binds to the synaptic vesicle protein 2A (SV2A) receptors on glutamate-containing transmitter vesicles, where it is believed to inhibit excitatory neurotransmitters release (vesicular exocytosis) and thereby reduce synaptic excitability. Retigabine opens KCNQ2-5 (Kv7.2-Kv7.5) voltage-gated potassium channel in presynaptic nerve terminals and thereby inhibits glutamate release. In addition to its action on calcium and sodium channel, valproate may enhance voltage-gated potassium channel permeability, causing hyperpolarization. Perampanel is a potent noncompetitive antagonist of the AMPA receptors, a subtype of the ionotropic glutamate receptors that are the primary mediators of synaptic excitation in the central nervous system. Phenobarbital may block glutamate AMPA receptors and its action on voltage-activated calcium channel and GABA-chloride ion channel. Felbamate blocks glutamate NMDA receptors, with selectivity for those containing the GluN2B subunit. The drug also produces a barbiturate-like potentiation of $GABA_A$ receptor responses. The possible sites for the action of topiramate

include voltage-gated sodium channel, $GABA_A$ receptor subtypes, and glutamate AMPA receptors.[31]

1.11 | Principles of ASD selection for specific seizure type(s)

Treatment should be considered in patients reporting more than one unprovoked seizure or after a single seizure if the risk of recurrence is high.[1] The initial ASD should be individualized on the basis of seizure type and/or epilepsy syndrome and slowly titrated up to a target dosage. Other important selection criteria include patient characteristics, drug efficacy, adverse-effect profile, potential drug-drug interactions, and cost.[32] Combination therapy should be considered after the failure of two monotherapies.[33] The therapeutic spectrum of ASDs can be categorized into (1) broad-spectrum drugs used for both focal and generalized seizures, including, in alphabetical order, brivaracetam, clobazam, felbamate, lamotrigine, levetiracetam, perampanel, rufinamide, topiramate, valproate, and zonisamide; (2) narrow-spectrum drugs used primarily for focal and focal to bilateral (secondarily generalized) tonic-clonic seizures including carbamazepine, cenobamate, eslicarbazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, stiripentol, tiagabine, and vigabatrin; and (3) a narrow-spectrum drug used primarily for generalized absence seizures which is ethosuximide.

Table 3 presents the efficacy of ASDs against common seizure types and epilepsy syndrome. The data supplemented in the table are based primarily on the results of RCTs comparing the newer versus older drugs, including the SANAD studies[34-37] and others,[38-62] and recently published meta-analyses.[63-69] Table 4 and the remainder sections of this article present guidance for ASD selection for the specific seizure type according to the 2017 ILAE classification of seizure types and epilepsy syndromes.[14-17] The guidance is based mainly on the current state of the literature on the efficacy and tolerability of ASDs and the recently published practical guidelines. The most popular treatment guidelines applied herein are the guidelines published by AAN & AES in 2004, 2015, and 2018,[12,13,21,22,70] the ILAE in 2006 and 2013,[71,72] the UK National Institute for Health and Care Excellence in 2012,[73,74] and the Scottish Intercollegiate Guidelines Network in 2018.[75,76]

1.12 | Drugs effective for focal-onset seizures

Focal-onset seizures account for 60% of all epilepsies. The RCTs and meta-analyses have demonstrated comparable efficacy of several ASDs in controlling new-onset focal seizures.[22,34,37-44,46,58,62-64,72,77-83] The drug of the first choice for "focal" and "focal to bilateral" (secondarily generalized) tonic-clonic seizures is lamotrigine.[22,34,37] Phenytoin is the drug of choice for the urgent treatment of new-onset or recurrent focal epilepsy. The other most widely used first-line drugs for focal seizures include levetiracetam and zonisamide.[22,34] Carbamazepine is considered a second-line treatment for new-onset focal epilepsy owing to its unfavorable efficacy-to-tolerability profile.[22,34] Oxcarbazepine, topiramate, and valproate can be used, but they may not be as effective as lamotrigine and carbamazepine.[22] Phenobarbital (and its derivative primidone) is often regarded as a second-line treatment in adults because of sedation and behavioral problems.[22] However, phenobarbital is a primary drug for neonatal seizures.

Given the unique mechanistic and pharmacokinetic profiles of the third-generation ASDs, the United States Food and Drug Administration (FDA) recently issued a strategy that allows extrapolation of these drugs across populations as add-on or monotherapy.[22] Accordingly, brivaracetam, eslicarbazepine, lacosamide, and perampanel received FDA approval as initial monotherapies for new-onset focal epilepsy.[22] Individual monotherapy studies showed similar efficacy of second-generation (levetiracetam and zonisamide) and third-generation (eslicarbazepine and lacosamide) ASDs compared with controlled-release carbamazepine for the treatment of new-onset focal epilepsy.[63] Vigabatrin use appears to be less efficacious than carbamazepine use and may not be offered; furthermore, tolerability profile precludes vigabatrin use as first-line therapy.[22] The drugs used as add-on (adjunctive) therapy in focal seizures include gabapentin, pregabalin, felbamate, rufinamide, cenobamate, clobazam, retigabine, and tiagabine. However, the AAN/AES guidelines recommend gabapentin and lamotrigine, as first-line monotherapy in patients aged ≥60 years with new-onset focal epilepsy.[22] A recent systematic review and network meta-analysis showed that lacosamide, lamotrigine, and levetiracetam had the highest probability of ranking best for achieving seizure freedom in the elderly with new-onset epilepsy.[64] The FDA determined that the efficacy of ASDs for focal-onset seizures in adults can be extrapolated downward to children four years of age and above.[22]

For drug-resistant focal epilepsy in adults, eslicarbazepine can be used as monotherapy while the immediate-release pregabalin, perampanel, lacosamide, eslicarbazepine, extended-release topiramate, rufinamide, clobazam, felbamate, and vigabatrin should be considered as add-on therapy.[21] However, vigabatrin, felbamate, and rufinamide are not first-line agents because of the retinopathy risk with vigabatrin, the modest benefit with rufinamide, and the hepatotoxicity and hematotoxicity risk with felbamate. In pediatric patients, levetiracetam, oxcarbazepine, and zonisamide should be considered as add-on therapy.[21]

1.13 | Drugs effective for generalized tonic-clonic seizures (GTCS)

There has been a limited number of ASDs that can be used as first-line agents for GTCS. Valproate remains the first-line drug for many patients with generalized and unclassified epilepsies,[22,35,36,72] while phenobarbital (or primidone) is a primary drug in infants (for neonatal seizures) and an alternative in adults. However, valproate should not be prescribed for women of childbearing potential because of

its dose-dependent teratogenic profile; unless other ASDs cannot control the seizures, in which case the dose should be kept as low as possible.[84] Indeed, some patients with genetic generalized epilepsy can control their seizures only with valproate. The other most widely used monotherapies for GTCS include lamotrigine, levetiracetam, brivaracetam, topiramate, clobazam, and zonisamide.[22] However, there appears to be no evidence to support any second-generation or third-generation ASDs to be as efficacious as valproate monotherapy for generalized and unclassified epilepsies.[35,36] The combination of lamotrigine and valproate is believed to be particularly efficacious.[85] Phenytoin and carbamazepine are effective but may worsen certain seizure types in generalized epilepsies, including absence epilepsy, juvenile myoclonic epilepsy, and Dravet's syndrome.[86] Vigabatrin, tiagabine, oxcarbazepine, and possibly gabapentin are other drugs that may worsen these seizure types. Seizures of most patients with generalized epilepsy are easily controlled with appropriate medication. However, immediate-release and extended-release lamotrigine use should be considered add-on therapy to decrease seizure frequency in drug-resistant GTCS in adults.[21] Levetiracetam should also be effective in both drug-resistant GTCS and drug-resistant juvenile myoclonic seizures. Other drugs used as add-on therapy in GTCS include perampanel and lacosamide.

1.14 | Drugs effective for focal seizures and certain generalized onset seizure types

A variety of drugs are primarily used to treat focal seizures; these drugs have also been effective in certain generalized onset seizure types. These drugs are lamotrigine, levetiracetam, brivaracetam, perampanel, phenobarbital, primidone, and felbamate.

1.15 | Drugs effective for myoclonic seizures

Valproate is widely used for myoclonic seizures, such as in juvenile myoclonic epilepsy.[87] Lamotrigine is possibly effective but may worsen myoclonic seizures in some cases. Other drugs effective in treating this seizure type are levetiracetam, brivaracetam, zonisamide, topiramate, and clonazepam.

1.16 | Drugs effective for generalized absence seizures

Ethosuximide is the first-line drug. It is often used in uncomplicated absence seizures if patients can tolerate its gastrointestinal side effects.[22,45] Despite the long half-life (~ 40 hours), ethosuximide is generally administered in two or even three divided doses to minimize the adverse gastrointestinal effects. Valproate is preferred in patients with concomitant GTCS or myoclonic seizures (myoclonic absence seizure). Clonazepam is effective as an alternative drug but has the disadvantages of causing sedation and tolerance. Lamotrigine, levetiracetam, and zonisamide are also used in the absence seizures but not as effective as ethosuximide or valproate. Unless there are compelling reasons based on adverse events profile, ethosuximide or valproate use should be considered before lamotrigine in treating absence seizures.[45] Lamotrigine should be considered in women of childbearing age because of its better tolerability and fewer fetal risks compared with valproate.

1.17 | Drugs effective for other epilepsy syndromes

In combination with lamotrigine and a benzodiazepine (such as clobazam), valproate is the most widely used treatment for atonic seizures (eg, in the Lennox-Gastaut syndrome). Other drugs used for the atonic seizures in Lennox-Gastaut syndrome include topiramate, felbamate, and rufinamide.[85] Because felbamate can cause aplastic anemia and severe hepatitis, it is used as add-on therapy in patients who respond poorly to other agents. For infantile spasms (West's syndrome), valproate, topiramate, zonisamide, or a benzodiazepine (such as clonazepam or nitrazepam) is effective.[85] Vigabatrin and everolimus are used if associated with tuberous sclerosis complex (a rare genetic disease that causes noncancerous (benign) tumors to grow in the brain and other organs). However, infantile spasms are primarily treated with intramuscular adrenocorticotropic hormone (ACTH) or oral corticosteroids such as prednisone or hydrocortisone (unknown mechanism). For Dravet's syndrome (the severe myoclonic epilepsy of infancy), valproate, topiramate, and clobazam can be used, although none of these is very effective.[88] Stiripentol, a modulator of $GABA_A$ receptors, is often used in conjunction with clobazam or valproate.[88] Cannabidiol was approved in 2018 to treat Dravet's syndromes[66] in addition to Lennox-Gastaut syndrome[68] and infantile spasms associated with tuberous sclerosis complex. Recent meta-analyses showed that adjunctive cannabidiol was associated with a greater reduction in convulsive seizure frequency than placebo in patients with Lennox-Gastaut syndrome[68] and children with Dravet syndrome.[66] Fenfluramine is another new drug approved in 2020 for Dravet's syndrome. The drug is available only through a restricted drug distribution program, under a risk evaluation and mitigation strategy (REMS) because of the risk of valvular heart disease and pulmonary arterial hypertension. Recent studies, however, showed that fenfluramine provided a significantly greater reduction in convulsive seizure frequency compared with placebo and was generally well tolerated, with no observed valvular heart disease or pulmonary arterial hypertension.[65,89]

1.18 | Drugs effective for status epilepticus

Status epilepticus (SE) is a life-threatening emergency that requires immediate treatment.[90] In clinical practice, it is now generally accepted that a seizure lasting >5 minutes for GTCS and 10 minutes for focal seizures with or without impairment of consciousness should

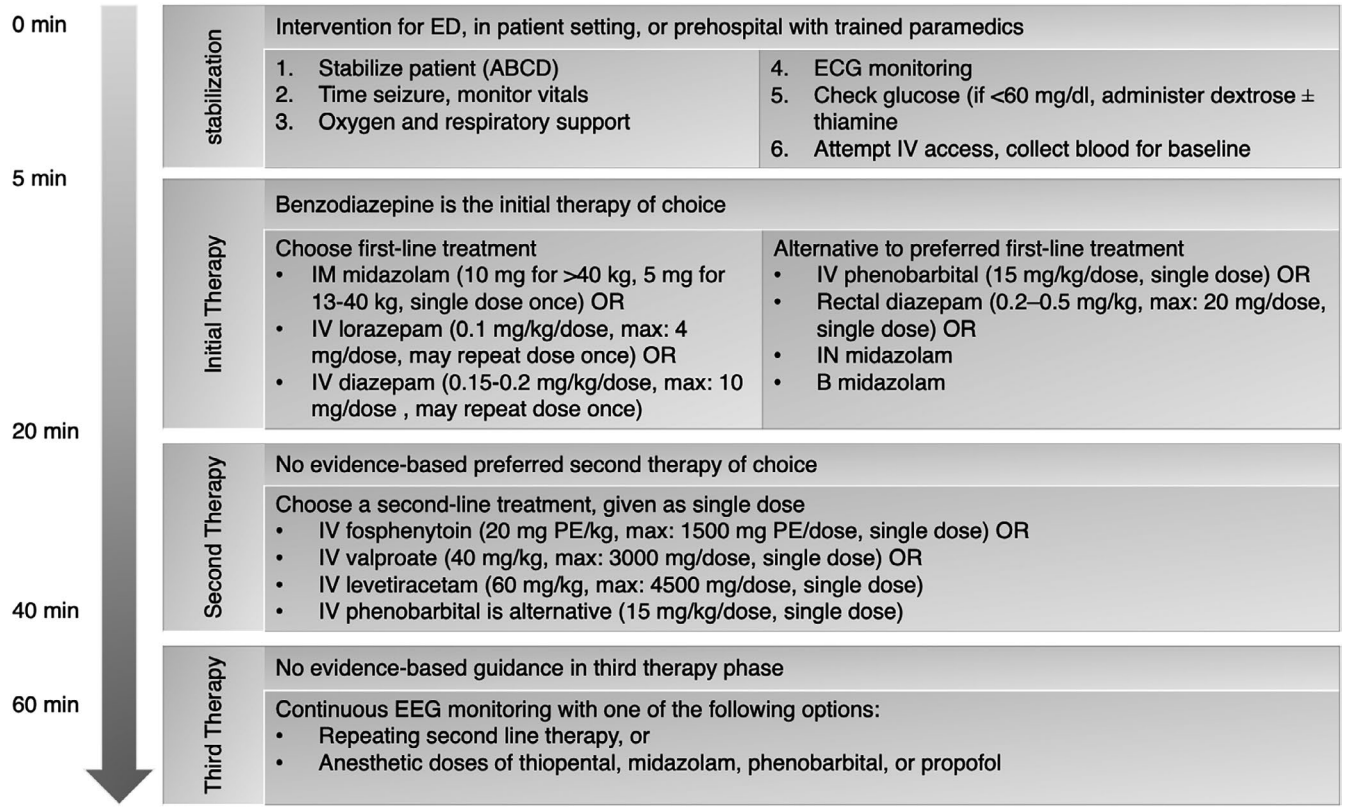

FIGURE 2 Status Epilepticus treatment algorithm*

*Adopted from Glauser T, et al *Epilepsy Curr*. 2016; 16:48-6. Refer to publication for complete recommendations.

ABCD, airway, breathing, circulation, disability (Neurologic); B, buccal; ECG, electrocardiogram; ED, emergency department; EEG, electroencephalogram; IM, intramuscular; IN, intranasal; IV, intravenous; PE, phenytoin sodium equivalents; SE, status epilepticus.

be treated as status epilepticus. Figure 2 presents the SE treatment algorithm. According to the evidence-based guideline for the treatment of convulsive SE in children and adults by the AES in 2016,[91] the first-line treatment for SE is a benzodiazepine (either intravenous lorazepam or intravenous diazepam or intramuscular midazolam). If the preferred options are not available, rectal diazepam, intranasal midazolam, buccal midazolam, or intravenous phenobarbital is acceptable alternatives.

If the seizure continues, then second-line treatment is administered.[69] Intravenous fosphenytoin is preferred over phenytoin as the latter may cause cardiotoxicity. With phenytoin intravenous administration, there is also a risk of the potentially serious "purple glove syndrome," in which a purplish-black discoloration accompanied by edema and pain occurs distal to the site of injection. Fosphenytoin has a lower incidence of purple glove syndrome. The second-line treatment also includes intravenous valproate or intravenous levetiracetam. Intravenous phenobarbital can be alternative (if not given already) but has a long half-life causing persistent adverse effects, including severe sedation, respiratory depression, and hypotension. A recent network meta-analysis compared efficacy and tolerability of intravenous valproate, phenytoin, diazepam, phenobarbital, lacosamide, and levetiracetam in adults with benzodiazepine-resistant convulsive SE and suggested that phenobarbital had the greatest probabilities of being best in the achievement of SE control and seizure freedom, whereas valproate and lacosamide ranked best for the safety outcomes (respiratory depression and hypotension).[69]

If the second therapy fails to stop the seizures, another second-line agent is often tried. Treatment-resistant SE occurs when seizures continue or recur at least 30 minutes after treatment with first- and second-line agents and should be treated with anesthetic doses of pentobarbital, propofol, midazolam, or thiopental. Dosing and frequency are available in the proposed algorithm for convulsive SE.[91] Acute repetitive seizures (seizure clusters), in which there is complete recovery between seizures, are treated with benzodiazepines. Diazepam rectal gel is the only approved treatment for the out-of-hospital treatment of acute repetitive seizures.[92]

1.19 | Adverse effects of ASDs

The adverse effects of selected ASDs are listed in Table 5. The first-generation ASDs have acute dose-related effects, primarily neurological effects such as sedation, dizziness, unsteadiness, blurred vision, diplopia, and tremor, in addition to neurocognitive and psychiatric symptoms.[25,26,32] These effects are found across the different ASDs[26,62] and often mild and reversible. However, some drugs are better tolerated than others; for example, lamotrigine and levetiracetam are better tolerated than carbamazepine in elderly

TABLE 1 Pharmacokinetic profiles of antiseizure drugs

Antiseizure drug	Bioavailability %	Peak concentration (hr)	Plasma protein binding (%)	Elimination half-life (hr)	Route of elimination	Therapeutic serum concentration (mcg/mL)
Brivaracetam	~ 95	1	≤ 20	7-10	++	0.2-2
Carbamazepine	75-85	4-5	70-80	10-17	++++	4-11
Cannabidiol	10-20	2.5-5	>94	56-61	++++	NE
Cenobamate	88	1-4	60	50-60	+++	NE
Clobazam	90-100	1-3	80-90	36-42	++++	0.03-3
Clonazepam	>80	1-4	80-90	24-48	+++	10-70[a]
Eslicarbazepine	>90	1-4	<40	13-20	++++	5-35
Ethosuximide	95-100	3-7	0	30-60	++	40-100
Felbamate	>90	3-5	22-36	16-22	++	30-60
Gabapentin	50	2-3	0	5-9	-	3-21
Lacosamide	100	1-2	<30	12-14	+	3-10
Lamotrigine	~ 90	1-3	55	8-35	+++	3-13
Levetiracetam	~ 95	1-2	<10	6-8	-	5-41
Oxcarbazepine	100	4-5	75	10-17	++++	3-36
Perampanel	100	0.5-3	95-96	70-110	+++	0.1-1
Phenobarbital	>90	0.5-4	55	90	++	12-30
Phenytoin	85-90	5-7	90	24	+++[b]	10-20
Pregabalin	~90	1-2	0	4.5-7	-	2-6
Primidone	>90	2-6	10	8-15	++	8-12
Rufinamide	>90	4-6	35	6-10	++	4.5-31
Stiripentol	Variable	2-3	99	4.5-13	+	4-22
Tiagabine	~90	0.5-2	96	2-9	+++	0.02-0.2
Topiramate	~80	2-4	15	20-30	+	2-10
Valproate	>90	2-4	90	15	++++	50-100
Vigabatrin	100	1	0	5-8	-	20–160[a]
Zonisamide	>90	2-6	40-60	50-68	++	10-38

Note: NE, not established

++++Extensive hepatic metabolism and active metabolite(s)

+++Extensive hepatic metabolism but no active metabolite(s)

++Hepatic metabolism (with or without active metabolites) and renal excretion.

+Variable (or moderate) hepatic metabolism (with or without active metabolites)

-Renal excretion (unchanged). No hepatic metabolism

[a]ng/mL

[b]Saturable

patients.[93] Psychiatric adverse effects include depression, anxiety, irritability, impaired concentration, mood changes, hyperactivity, and, in rare cases, psychosis. Although the newer ASDs are touted as better tolerated than older drugs,[12] psychiatric adverse effects are common with levetiracetam, topiramate, zonisamide, vigabatrin, and perampanel. Lamotrigine, carbamazepine, valproate, gabapentin, and pregabalin, in contrast, have mood-stabilizing effects in some patients and less frequently cause behavioral or psychiatric effects.[94]

Most women with epilepsy who become pregnant require continued ASD therapy for seizure control. If possible, valproate, carbamazepine, phenytoin, phenobarbital, and topiramate should be avoided in women of childbearing potentials. Recent analysis from several international pregnancy registers suggests that in utero exposure to valproate during the first trimester is associated with a threefold increased risk of congenital malformations, commonly neural tube defects (spina bifida) and cardiovascular, orofacial, and digital abnormalities.[95] The use of valproate during the first trimester is also associated with cognitive impairments. Carbamazepine may cause neural tube defects and craniofacial anomalies. Fetal hydantoin syndrome is related to the use of phenytoin. Treatment with topiramate during the first trimester of pregnancy is associated with a 10-fold increase in oral clefts risk. Phenobarbital can cause congenital malformations, most often cardiac defects. No ASD is known to be entirely safe for the developing fetus. However, lamotrigine and levetiracetam have the

TABLE 2 Mechanistic categorization of current antiseizure drugs based on foremost targets at therapeutic concentrations

Target and mechanism[a]	Antiseizure drug
Inhibition of voltage-gated sodium channels	Phenytoin, fosphenytoin, carbamazepine, cenobamate, lamotrigine, oxcarbazepine, eslicarbazepine, lacosamide, and possibly topiramate, zonisamide, rufinamide, and phenobarbital
Inhibition of α2δ subunit of voltage-gated calcium channels	Gabapentin, pregabalin
Inhibition of T type voltage-gated calcium channels	Ethosuximide
Activation of $GABA_A$ receptor	Phenobarbital, benzodiazepines, and possibly topiramate, felbamate, retigabine, and stiripentol.
Inhibition of GABA transporter (selective)	Tiagabine
Inhibition of GABA transaminase enzyme	Vigabatrin
Modulation of synaptic vesicle protein 2A	Levetiracetam, brivaracetam
Various actions on multiple targets	Valproate, felbamate, topiramate, zonisamide, and cannabidiol
Opening KCNQ2-5 (Kv7.2-Kv7.5) voltage-gated potassium channels	Retigabine (ezogabine)[b]
Inhibition of NMDA-type glutamate receptors	Felbamate, topiramate and phenobarbital
Inhibition of AMPA-type glutamate receptors	Perampanel

[a]Fenfluramine's mechanism of action for the treatment of seizures associated with Dravet syndrome is unknown.

[b]Production of the drug retigabine has been discontinued by the manufacturer, and it is no longer available.

lowest risks of major congenital malformations and may be safer, particularly for cognition compared with valproate.[85]

Valproate causes hepatotoxicity in children less than two years of age. Carbamazepine and lamotrigine may cause life-threatening Steven-Johnson syndrome and toxic epidermal necrolysis, which is strongly associated with the HLA-B*1502 allele. Asians, who have a 10-fold increased risk of the drug-induced Stevens-Johnson syndrome compared with other ethnic groups, should be tested before starting the drug. The use of zonisamide is also associated with severe skin reactions. Aplastic anemia and acute hepatic failure have limited the use of felbamate to severe and drug-resistant epilepsy. Overdose toxicity with benzodiazepines and barbiturates may cause respiratory depression. Management is primarily supportive (airway management, mechanical ventilation) and flumazenil in benzodiazepine overdose. Withdrawal from ASDs should be accomplished gradually (over a 1- to 3-month period or longer) to avoid the occurrence of severe seizures or status epilepticus. Physical dependence occurs with barbiturates and benzodiazepines, and there is a well-recognized risk of rebound seizures with abrupt withdrawal. However, withdrawal is less likely to be a problem with ethosuximide. Withdrawal is believed to be successful in patients with generalized epilepsies who exhibit a single seizure type, whereas the longer duration of epilepsy, an abnormal neurologic examination, an abnormal EEG, and certain epilepsy syndromes, including juvenile myoclonic epilepsy, are associated with increased risk of recurrence.[85]

Clinical studies suggest a possible association of lamotrigine, levetiracetam, and topiramate with suicidality. In 2008, the FDA issued an alert that ASDs, as a class, may be associated with an increased risk of suicidality based on an analysis of data from placebo-controlled add-on clinical trials of ASDs in patients with drug-resistant epilepsy, although this is still highly controversial.[96,97] Long-term treatment with ASDs is associated with a twofold to threefold increased risk of osteoporosis and bone fractures.[98] In addition, increased body weight and fat are common in patients using valproate, carbamazepine, gabapentin, pregabalin, vigabatrin, and perampanel and can lead to serious health consequences associated with obesity and increased cardiovascular disease risk.[99] In March 2021, the FDA issued an alert that lamotrigine may be associated with an increased risk of cardiac arrhythmias in people with underlying cardiac disease.[100] However, this risk is not apparent in healthy individuals.[101]

1.20 | The new frontiers in epilepsy pharmacology

Since 1989, nearly 20 second-generation and third-generation antiseizure drugs (ASDs) with different mechanisms of action have reached the market, resulting in a greatly increased range of treatment options for patients and prescribers.[102,103] Some second-generation ASDs have shown advantages in drug tolerability, drug-drug interactions, and teratogenicity and thus offer valuable individualized options in treating epilepsy. Disappointingly, however,

TABLE 3 Efficacy of antiseizure drugs against common seizure types and epilepsy syndromes

Antiseizure drug/ seizure type	Focal seizures	GTCS	Absence	Myoclonic	Lennox–Gastaut syndrome	Infantile spasm	Dravet's syndrome
Brivaracetam	+	+		+			
Cannabidiol					+	+[a]	+
Carbamazepine	+	+	–	–			–
Cenobamate	+						
Clobazam	+	+			+		+[e]
Clonazepam			+	+		+	
Eslicarbazepine	+		–	–			
Ethosuximide			+				
Felbamate	+[b]				+		
Fenfluramine							+
Gabapentin	+	?+	–	–			–
Lacosamide	+	?+					
Lamotrigine	+	+	+	?+[c]	+		
Levetiracetam	+	+	?+	+			
Oxcarbazepine	+	+	–	–			–
Perampanel	+	+					
Phenobarbital	+	+	–	?+			
Phenytoin	+	+	–	–			–
Pregabalin	+			–			
Primidone	+	+	–				
Retigabine[g]	+						
Rufinamide	+				+		
Stiripentol							+[f]
Tiagabine	+		–	–			
Topiramate	+	+		+	+	+	+[e]
Valproate	+	+	+	+[d]	+	+	+[e]
Vigabatrin	+	?+	–	–		+[a]	
Zonisamide	+	+	?+	+		+	

Note: GTCS; generalized tonic-clonic seizure

Note that although there is evidence to support the use of these drugs for these seizure types, the drugs may not be indicated for this use by the US Food and Drug Administration.

+Effective;?+ possibly effective; – worsen seizure.

[a]Especially when associated with tuberous sclerosis complex.

[b]Can cause aplastic anemia and severe hepatitis, used only for patients who respond poorly to other agents.

[c]Possibly effective but may worsen myoclonic seizures in some cases.

[d]Preferred in patients with concomitant GTCS or myoclonic seizures (myoclonic absence seizure).

[e]None of these is very effective in Dravet's syndrome.

[f]In combination with clobazam and valproate.

[g]Has been discontinued by the manufacturer, and it is no longer available.

none of these medications appear to be more efficacious than first-generation ASDs, and none have substantially reduced the proportion of patients with drug-resistant epilepsy, highlighting the need for novel strategies in epilepsy drug development. Given the favorable pharmacokinetic characteristics and adverse-effect profiles for the third-generation medications, additional evidence to further define their efficacy is crucial to the future treatment of epilepsy. The high incidence of drug-resistance and unwanted adverse effects caused by taking long-term ASDs raise substantial concern. In particular, there is an urgent need for developing novel drugs that act beyond the membrane ion channels and neural transmissions. Deciphering the genetics that underpins the mechanisms that generate seizures is one of the promising areas in the field.[104] Many epilepsy genes have been identified, including genes that increase the risk of different types of epilepsy, such as generalized and focal epilepsy and developmental and epileptic encephalopathies. These genes have

TABLE 4 Recommendations for add-on and monotherapy in adults and pediatric patients >4 years of age with new-onset epilepsy based on an assessment of current literature and published guidelines

Seizure type	First-line (Monotherapy or add-on)	Second-line (Monotherapy or add-on)	Third-line (Add-on)
Focal-onset seizures, including focal to bilateral tonic-clonic seizure	Lamotrigine[a]	Carbamazepine Levetiracetam Zonisamide Phenytoin Valproate Topiramate[b] Oxcarbazepine[b] Gabapentin[b] Phenobarbital[c] Brivaracetam[d] Eslicarbazepine[d] Lacosamide[d] Perampanel[d]	Cenobamate[e] Clobazam Retigabine Felbamate Rufinamide Pregabalin Tiagabine Vigabatrin
Generalized tonic-clonic seizures (GTCS)	Valproate[f]	Carbamazepine Phenytoin Lamotrigine Topiramate Levetiracetam Brivaracetam Perampanel Zonisamide Clobazam Phenobarbital	
Myoclonic seizure	Valproate	Lamotrigine[g] Topiramate Levetiracetam Brivaracetam Clonazepam Zonisamide	
Absence seizures	Ethosuximide Valproate	Lamotrigine Clonazepam Levetiracetam	
Unclassified seizures[h]	Valproate	Lamotrigine Levetiracetam Topiramate Zonisamide	

[b]Evidence is insufficient to consider gabapentin, oxcarbazepine, or topiramate instead of lamotrigine in patients with new-onset focal epilepsy. Gabapentin may be considered first-line monotherapy in patients aged ≥60 years.

[c]Often regarded as second-line treatment in adults because of sedation and behavioral problems.

[d]Received FDA approval for extrapolation of efficacy as monotherapy across individuals with focal seizures (Kanner AM, et al *Neurology* 2018; 91:82-90).

[e]Evidence is insufficient to consider the use of clobazam, felbamate, tiagabine, vigabatrin, or third-generation antiseizure drugs as monotherapies in treating new-onset focal epilepsy.

[f]Valproate should be avoided, if possible, in women of childbearing potential.

[g]May worsen myoclonic seizures in some cases.

[h]Evidence is insufficient to support efficacy of newer antiseizure drugs in unclassified generalized tonic-clonic seizures.

[a]Lamotrigine was superior to levetiracetam and zonisamide for time to 12-month remission and should remain a first-line treatment for new-onset focal epilepsy.

a role in ion channel and synaptic dysfunction in addition to transcriptional regulation. Most mutations occur in the protein-coding exons, the sodium and potassium channel, and glutamate receptors.[32] Ganaxolone, sirolimus, everolimus, cannabidiol, fenfluramine, stiripentol, and memantine are new selective disease-modifying therapies recently approved for severe forms of genetic epilepsies.[32] Data to support gene-therapy treatments need to be established in future research, and there are often other disorders that these therapies can improve, including acquired epilepsies.[104] Furthermore, with a deeper understanding of the cellular and molecular mechanisms of epileptogenesis, non-classical novel antiseizure agents, such as neurosteroid and allopregnanolone, with their effect on both GABAergic and

TABLE 5 Common and serious adverse effects of selected antiseizure drugs

Antiseizure drug	Systemic adverse effects	Neurologic adverse effects	Rare idiosyncratic reactions
Brivaracetam	Nausea, vomiting, constipation, fatigue	Headache, somnolence, dizziness, abnormal coordination, nystagmus, mood changes	
Carbamazepine	Nausea, vomiting, diarrhea, a plastic anemia, leukopenia, hyponatremia (common reason for discontinuation), hepatotoxicity, rash, pruritus	Ataxia, dizziness, blurred vision, diplopia, headache	Erythematous maculopapular rash (Steven-Johnson syndrome and toxic epidermal necrolysis), teratogenicity
Cenobamate	Nausea, vomiting, fatigue, hyperkalemia, QT shortening	Somnolence, dizziness, headache, balance disorder, diplopia	Drug reaction with eosinophilia and systemic symptoms (DRESS)/ multiorgan hypersensitivity (at high doses)
Eslicarbazepine	Nausea, vomiting, diarrhea, hyponatremia, rash	Dizziness, drowsiness, headache, somnolence, diplopia, ataxia, blurred vision, tremor	
Ethosuximide	Nausea, vomiting	Sleep disturbance, drowsiness, hyperactivity	
Felbamate	Nausea, vomiting, anorexia, weight loss	Insomnia, dizziness, headache, ataxia	Aplastic anemia, severe hepatitis/ hepatic failure
Gabapentin	Infrequent	Somnolence, dizziness, ataxia, headache, tremor, and fatigue	
Lacosamide	Nausea, vomiting, increased cardiac conduction (PR interval)	Dizziness, ataxia, diplopia, headache	
Lamotrigine	Nausea, rash, cardiac arrhythmias	Dizziness, tremor, diplopia	Steven-Johnson syndrome
Levetiracetam	Fatigue, infection, anemia, leukopenia	Somnolence, dizziness, agitation, anxiety, irritability, depression, psychosis	
Oxcarbazepine	Nausea, rash, hyponatremia (more common)	Somnolence, headache, dizziness, vertigo, ataxia, diplopia	
Perampanel	Weight gain, fatigue, nausea	Dizziness, somnolence, irritability, gait disturbance, falls (with high dose), aggression, mood alteration	
Phenobarbital	Nausea, rash	Somnolence, ataxia, dizziness, confusion, cognitive dysfunction, tolerance, dependence	
Phenytoin	Gingival hyperplasia, hirsutism, megaloblastic anemia, peripheral neuropathy, osteoporosis, rash	Nystagmus (early sign of phenytoin administration), diplopia, ataxia, somnolence	
Pregabalin	Weight gain, peripheral edema, dry mouth	Somnolence, dizziness, ataxia, headache, and tremor	
Rufinamide	Nausea, vomiting, leukopenia, cardiac conduction (QT interval shortening)	Somnolence, fatigue, dizziness, ataxia, headache, diplopia	
Tiagabine	Abdominal pain, nausea, lack of energy	Dizziness, difficulty concentrating, somnolence, nervousness, tremor, language problems	
Topiramate	Anorexia, weight loss, paresthesia, fatigue	Nervousness, psychomotor slowing, language problems, depression, anxiety, mood problems, tremor	Acute glaucoma (may require prompt drug withdrawal).
Valproate	Gastrointestinal irritation, weight gain, hair loss, easy bruising	Ataxia, somnolence, tremor	Hepatotoxicity, teratogenicity, and thrombocytopenia
Vigabatrin	Fatigue	Somnolence, headache, dizziness, agitation, confusion, psychosis.	Irreversible bilateral concentric visual field defect
Zonisamide	Weight loss, nausea, anorexia	Somnolence, dizziness, confusion, headache, psychosis	Potentially serious skin rashes

glutaminergic systems, may shed light on finding a new approach to treat epilepsy, which is not only controlling seizures but also retarding epileptogenesis.[105] Novel pharmacological approaches built on gene therapies and epileptogenesis may overcome many of the adverse effects of currently available treatment options.

2 | CONCLUSIONS

Antiseizure drugs (ASDs) have many different pharmacologic profiles that are relevant when selecting and prescribing these medications in patients with epilepsy. These include pharmacokinetic properties, propensity for drug-drug interactions, and adverse-effect profile and toxicities. This article reviewed the current state of the literature about the clinical pharmacology of ASDs, based primarily on the most recent evidence for the efficacy and tolerability of the currently available drugs and the recent US and UK treatment guidelines. It is anticipated that Table 4 in this review (recommendations for ASD selection) will require updating as future studies yield more detailed results. It is hoped that this review remains a succinct and practical guide to assist non-neurologists, particularly the primary healthcare practitioners, in patient care decisions. The medical students may also wish to read this review to improve their understanding of epilepsy and its pharmacological treatment. Finally, the content of this review is not intended to include all legitimate criteria for choosing to use or exclude a specific drug, nor recommended as a substitute for current scientific and clinical information. Physicians are encouraged to carefully review the literature in addition to the full guidelines to understand all recommendations associated with patient care and be confident that the information contained in this work is accurate, particularly for new or infrequently used drugs. Physicians are also encouraged to obtain information about drug dosing and frequency from the product information sheet included in each drug package. Complete information on US Food and Drug Administration (FDA) labeling for each drug can be accessed using the FDA searchable database (FDALabel).

CONFLICT OF INTEREST

The author declares no conflict of interest.

AUTHOR CONTRIBUTIONS

The author has made substantial contributions to the conception and design of the work, and acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article.

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How to cite this article: Hakami T. Neuropharmacology of Antiseizure Drugs. Neuropsychopharmacol Rep. 2021;41: 336–351. https://doi.org/10.1002/npr2.12196