

Innovations in Epilepsy Management – An Overview

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ABSTRACT - In the past twenty years, thirteen new antiepileptic drugs (AEDs) have been introduced, each differing in their efficacy spectrum, mechanism of action, pharmacokinetics, safety and tolerability profiles. These newer AEDs symbolize a welcoming future in the management of epilepsy because they are able to produce a remarkable reduction in seizure frequency in up to 40% to 50% of the patients who had been refractory to old generation drugs. Despite the current availability of these new drugs, only a few patients with truly refractory seizures can be made seizure free. Although the newer agents are not superior to that of the older drugs, some have been shown to be non-inferior in terms of their efficacy. They offer additional advantages like better tolerability, ease of use, reduced interaction profile. Even though in most situations the older generation drugs still represent the best choice, advancing studies show that in many conditions, new generation drugs may be entirely vindicated for initial therapy. This urges a need for the search of novel and more efficacious new antiepileptic drugs in the management of uncontrollable seizures. More direct comparisons of newer versus newer and newer versus older drugs in clinical trials, both for monotherapy and adjunctive therapy must be conducted. More than 20 compounds with promising antiepileptic and neuroprotective properties have been discovered and are under various stages of drug development.

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INTRODUCTION

Epilepsy is regarded as the most common serious neurologic disorder and affects about 0.5% of the population. Even though most people with epilepsy can be made seizure free and can lead a normal life with currently available appropriate drug therapy, 30% to 40% of patients continue to have seizures despite the use of antiepileptic drugs (AEDs), either as monotherapy or in combination (1). Uncontrolled seizures, particularly generalized convulsive seizures, pose a serious threat because they are associated with an increased risk of morbidity and mortality. Moreover, patients with refractory epilepsy face a psychosocial burden because of stigma, prejudice and discrimination (2).

Once a diagnosis of epilepsy has been made, pharmacotherapy is usually indicated. When considering AEDs, the patient's seizure type must be carefully evaluated (3). The medication chosen must be safe and effective for treating the specific type of seizure. Prior to 1993, the choice of AEDs was limited to phenobarbital, primidone, phenytoin, carbamazepine, valproate and ethosuximide (for

absence seizure). Although these traditional first generation AEDs have the benefit of being familiar and efficacious, many patients still experience refractory seizures as well as intolerable adverse effects. Since 1993, a new advent occurred in anti epileptic drug therapy with the approval of 10 new AEDs by the US Food and Drug Administration (FDA). The National Institute of Neurological Disorders and Stroke Anticonvulsant Screening Program (ASP) had provided direct preclinical support for these drugs in various stages of their development. They are oxcarbazepine, gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide, vigabatrin, and felbamate, in addition to the water-soluble phenytoin prodrug fosphenytoin (4, 5). These drugs produce a significant improvement in seizure control in many patients who had been refractory to the classical older drugs.

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The new generation AEDs offers the impending advantages of fewer drug interactions, unique mechanisms of action and a broader spectrum of activity; nevertheless they are much more expensive than standard drugs. With advancing treatment options, it is essential to determine the role of new AEDs in optimizing patient's drug therapy and understanding clinically significant adverse effects and drug interactions. The purpose of this article is to make primary care clinicians and health professionals acquainted with the efficacy and tolerability of the new AEDs which can facilitate the choice of appropriate drugs in the management of epilepsy.

Basic Treatment Principles

Each type of seizure has a specific drug that usually proves to be most effective and adequate (6). Therapy is initiated using a single drug preferred among the known appropriate AEDs. The dosage adjustments have to be done carefully based on clinical response to minimize potentially adverse consequences, chiefly with the aid of therapeutic drug monitoring because AEDs have a narrow therapeutic index and there are significant inter-individual variations in dose requirements (7, 8). If seizures cannot be controlled at the early target dosage, the dosage is then gradually increased until seizure freedom is attained or unbearable adverse effects occur (9, 10). If the initially prescribed drug

fails to control seizures, most clinicians choose to switch progressively to an alternative AED that can also be used as monotherapy. Combination therapy may be tried in patients refractory to two or three AEDs at maximum tolerated doses given as monotherapy. This usually exposes the patient to a greater trouble in terms of side effects, increased risk of drug interactions, poor prognosis and adherence to drug therapy. The main factors governing the selection of AEDs involves: spectrum of activity against different seizure types/epilepsy syndromes, efficacy in terms of the magnitude of clinical response in specific syndromes, patient's characteristics, side effect profile, interaction potential, ease of use, co-morbidity, availability or cost of medication (11). The choice of AEDs in the treatment of seizures is given in Table 1.

The old generation AEDs has complex pharmacokinetics. Among them, phenytoin, carbamazepine, phenobarbital and primidone are hepatic enzyme inducers (12). Only valproate, benzodiazepines and phenobarbital are considered to exhibit broad spectrum activity against partial and many generalized seizures, although barbiturates are ineffective against absence seizures. Some of the new relatively broad-spectrum AEDs, mainly lamotrigine, topiramate and zonisamide are useful particularly for patients with multiple seizure types as well as primarily generalized seizures. This

Table 1. AEDs used in different seizure types and epilepsy syndromes (WHO guidelines 2002)

Seizure type	First line agents	Alternatives
Partial	Carbamazepine, Phenytoin	Valproate, Phenobarbital, Topiramate, Lamotrigine, Vigabatrin, Gabapentin
Generalized tonic-clonic	Carbamazepine, phenytoin, valproate	Phenobarbital, topiramate, lamotrigine
Generalized myoclonic	Valproate, clonazepam	Phenobarbital, topiramate, lamotrigine
Generalized absence	Ethosuximide, valproate	Clonazepam, topiramate, lamotrigine
Generalized atonic/ clonic	Valproate	Clonazepam, nitrazepam, topiramate, lamotrigine
Infantile spasms	Vigabatrin	Valproate, Topiramate, lamotrigine
Dravet Syndrome	Valproate	Clobazam, Topiramate
Atonic, tonic, atypical absence in Lennox Gastaut Syndrome	Lamotrigine	Valproate, Topiramate, Felbamate

is mainly because some of these new agents tend to be better tolerated than second-line broad-spectrum drugs such as barbiturates and benzodiazepines (13). Because of the multiple seizure types in Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy) and its broad spectrum of activity, valproate is considered as the first drug of choice. Lamotrigine, topiramate and felbamate have been officially licensed for Lennox Gastaut Syndrome after demonstrating significant efficacy in randomized, double blind, placebo controlled studies. Vigabatrin is considered to be potential first-line drug against infantile spasms, particularly those associated with tuberous sclerosis in spite of its potential to induce irreversible visual field defects. Felbamate also has significant toxicity problems, and its use is restricted to those patients who are refractory to all other drugs. Other new AEDs have a narrower spectrum of efficacy, and they are mainly used in the treatment of partial seizures. Like carbamazepine and phenytoin, newer drugs (vigabatrin, tiagabine, gabapentin, and oxcarbazepine) may even aggravate certain generalized seizure types (14).

Recent FDA Approved AEDS

Since 2007, six new AEDs have been approved by the US FDA and European Medicine Agency (EMA). They are stiripentol, lacosamide, rufinamide, eslicarbazepine acetate, ezogabine (retigabine) and perampanel. These drugs have been found to have multiple mechanism and sites of action which altogether accounts for their observed clinical effects ie, efficacy, toxicity and tolerability.

Stiripentol was authorized by the EMA for adjunctive therapy with clobazam and valproic acid to treat refractory generalized tonic clonic seizures in young patients with Dravet syndrome (15). No other AED is found to possess antiepileptic potency comparable to stiripentol in Dravet syndrome (16). It potentiates γ -amino butyric acid (GABA) neurotransmission and prolongs the opening of δ -containing recombinant GABA_A receptors (17). It exhibits non linear pharmacokinetics (18). Neurobehavioural and gastrointestinal disorders are common during the stiripentol therapy. The most common adverse effects observed are drowsiness, tremor, ataxia, nausea and weight loss. Transient aplastic anaemia and leucopenia have also been reported (19, 20). Stiripentol is available as capsule (250 mg, 500 mg) and powder for oral suspension (250 mg, 500 mg).

Lacosamide was approved by FDA in 2008 for adjunctive therapy of partial onset seizures in patients of 17 years of age and over. It was the first AED to enhance the slow inactivation component of voltage gated sodium channels (21). Lacosamide also binds with collapsing response mediator protein, but it is uncertain whether it attributes to its antiepileptic activity. The most common side effects observed are dizziness, fatigue, nausea and ataxia. Lacosamide is undergoing phase III trials comparing its safety and efficacy with carbamazepine controlled release as monotherapy in newly or recently diagnosed patients with epilepsy aged 16 years and older. It has been under investigation for the treatment of generalized seizures in adults and children with epilepsy and also for the management of status epilepticus (22). The various dosage forms available are injection for intravenous use of strength 10 mg/ml, oral solution of 10 mg/ml and 50 mg, 100 mg, 150 mg and 200 mg tablets.

Rufinamide was approved by the FDA in 2008 for the adjunctive treatment of seizures associated with Lennox Gastaut syndrome in patients of age 4 years and older (22). It prolongs inactivated state of voltage gated sodium channels. The most common adverse effects observed are somnolence, dizziness, fatigue, headache, diplopia and gastrointestinal disturbances (23). It is under assessment by the FDA for adjunctive therapy for refractory partial seizures, generalized anxiety disorder and its efficacy in comparison to ketogenic diet in patients with drug resistant epilepsy. Its marketed dosage forms are 200 mg and 400 mg tablets.

Eslicarbazepine acetate was approved in European Union in 2009 for adjunctive therapy of partial seizures in adults (24). It inhibits sodium channel dependant release of neurotransmitters with similar potency to carbamazepine and oxcarbazepine. It has been associated with dizziness, somnolence, abnormal coordination, headache, diplopia, nausea and blurred vision (25). It is currently undergoing phase III trials in adults with partial onset seizures and in phase II trials for the treatment of bipolar disorder. The formulation available is tablet 800 mg.

Ezogabine (known as retigabine in Europe) is the first AED to target and open voltage gated potassium channel (Kv7). It was approved in 2011 as adjunctive therapy for patients over 18 years of age with partial seizures and refractory partial epilepsy. A notable side effect during retigabine

therapy is urinary retention due to the presence of voltage gated potassium channel subunits Kv7.2-Kv7.5 in the bladder urothelium (26). Side effects are generally dose related and include somnolence, dizziness and confusion. Available as tablet 50 mg, 100 mg, 200 mg, 300 mg and 400 mg.

Perampanel is the first α -amino hydroxyl methylisoxazole propionic acid (AMPA) glutamate receptor antagonist, approved first in Europe in July 2012. It was approved by FDA in October 2012 as adjunctive therapy for partial onset seizures with or without secondary generalized seizures in patients of 12 years of age and older (22). The frequent adverse effects observed are dizziness, gait disturbance, somnolence, fatigue, falls and suicidal behavior. There is only limited clinical experience available with this drug. It is available in the market as 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets.

Vigabatrin was approved by FDA in 2009 for adjunctive therapy of refractory complex partial seizures in adults and monotherapy of infantile spasms in infants of 1 month to 2 years of age (22). But it was first marketed in Europe in the late 1980s and was approved in Australia in 1993 and in Canada in 1994. Although vigabatrin is available in many countries, it has not previously been available in the US, because it has been associated with irreversible peripheral vision loss in many patients (27). It is an irreversible GABA transaminase inhibitor thereby increasing GABA levels in brain. It is available as 500 mg tablet and 500 mg powder for oral solution.

Clobazam was first approved in Australia in 1970; it has been used for years in Europe. It was approved by FDA in 2011 for adjunctive therapy of Lennox Gastaut syndrome in patients aged 2 years and older. Clobazam therapy has resulted in upto 70% reduction in drop seizures in these patients (28). It potentiates GABAergic neurotransmission by binding to the benzodiazepine site of the GABA_A receptor. It is often added to regimens including valproic acid, felbamate, lamotrigine or topiramate. It is under investigation for use as monotherapy for focal or generalized seizures in adults and adjunctive therapy for focal or generalized seizures in adults and children, for status epilepticus and febrile seizures (22). Adverse effects include drowsiness, dizziness, depression and aggressiveness. The formulation available is 5 mg, 10 mg and 20 mg tablets.

Efficacy of New Versus Old AEDS

Many studies have been done to compare the efficacy of new AEDs with that of the existing older agents.

Oxcarbazepine is equivalent to carbamazepine, valproic acid and phenytoin in efficacy. Lamotrigine is effective for newly diagnosed absence seizures in children. Topiramate and lamotrigine appear to be effective for adjunctive treatment of idiopathic generalized epilepsy in adults and children, as well as for the treatment of Lennox Gastaut syndrome. Gabapentin is effective for the treatment of mixed seizure disorders and gabapentin, lamotrigine, oxcarbazepine and topiramate are used for the treatment of refractory partial seizures in children (29, 30). Levetiracetam results in 50% reduction in partial seizure frequency and is effective as adjunctive therapy for refractory partial seizures (31). Lamotrigine has been found to have the highest 12 month seizure freedom rate (54%), followed by levetiracetam (43%) when compared with phenytoin and carbamazepine (32). Bruni et al (33) assessed the efficacy of vigabatrin as add-on therapy in patients with refractory partial epilepsy and found that it was well tolerated by 7.2% of patients receiving the drug. Topiramate use is more sustained in localization related epilepsy than in generalized epilepsy (34). It can be used as adjunctive therapy in children, adolescents and young adults with Lennox Gastaut syndrome (35). Topiramate at 100 mg and 200 mg is equivalent in efficacy and safety to 600 mg of fixed dose, immediate release carbamazepine administered in a BID regimen for partial seizures and to 1,250 mg fixed dose valproic acid for idiopathic generalized seizures (36). Zonisamide is useful as an initial monotherapy for newly diagnosed patients with partial epilepsy (37) and a better therapeutic alternative for the treatment of juvenile myoclonic epilepsy (38). Oxcarbazepine is effective as first line and add-on therapy for patients with partial seizures with or without secondarily generalized seizures and generalized tonic clonic seizures without partial onset (39).

The recent treatment guidelines developed by the American Academy of Neurology recommends the use of standard AEDs or the newer agents like oxcarbazepine, gabapentin, lamotrigine, topiramate as first line agents for patients with newly diagnosed epilepsy (40).

Safety and Tolerability of New Versus Old AEDS

Various studies had been conducted that compared the new generation AEDs with that of older agents in terms of their safety and tolerability profile. These studies concluded that the newer agents were found to be better tolerated than the old AEDs. Chadwick et al (41) reported that the discontinuation rate due to adverse effects in adolescents and adults newly diagnosed with partial or generalized epilepsy was found to be lower in the higher dosed gabapentin treated patients (13.5%) than among carbamazepine treated patients (24%) with dizziness, fatigue and somnolence more frequent in the carbamazepine treated group. Gabapentin doses >1,800 mg/day were as well tolerated as doses less than or equal to 1,800 mg/day and were associated only with asthenia, headache and dizziness in patients of age 12 years and older with a mean age of 37 years (42). Gabapentin has not been reported to cause blood dyscrasias, hepatotoxicity, Stevens-Johnson syndrome or serious hypersensitivity syndromes. In another study (43) that compared lamotrigine with phenytoin in patients of 14-75 years of age, a higher incidence of asthenia (29% versus 16%), somnolence (28% versus 7%) and ataxia (11% versus 0) was observed in the phenytoin treated group whereas 14% of patients on lamotrigine and 9% of those on phenytoin had a rash. Although lamotrigine is not associated with hepatotoxicity, it has the potential to cause serious hypersensitivity reactions which is proportional to the promptness of titration, decreasing age, and concomitant valproate use. Dizziness, nausea and headache have been associated with co-administration of lamotrigine and valproate. The risk of hospitalization for Stevens-Johnson syndrome or toxic epidermal necrolysis varies between 1 and 10 per 10,000 new users of all age groups for lamotrigine (44). When compared with valproate monotherapy, lamotrigine was not associated with weight gain and higher androgen levels in women of 15-50 years of age with epilepsy (45).

When the efficacy and safety of different doses of topiramate were compared with valproate and carbamazepine in children and adolescents with newly diagnosed epilepsy, the discontinuation rates due to adverse effects were found to be similar between the three, ranging between 19% and 28% in the topiramate treated, 23% in the valproate treated and 25% in the carbamazepine treated

groups (36). Cognitive problems associated with topiramate can occur mostly in a dose dependant manner in cognitively adult patients (46). Topiramate is not associated with blood dyscrasias. It may increase the risk of liver failure when given in combination with valproate (47). The most common idiosyncratic adverse event associated with topiramate use is nephrolithiasis, which may occur in 1.5% of patients with chronic use (48). Other side effects include parasthesias, hypohydrosis (especially in children) and metabolic acidosis.

Oxcarbazepine has low dose related adverse effects in children and adolescents with epilepsy when compared with carbamazepine, valproic acid and phenytoin (49). In a study (50) of adult patients with newly diagnosed, previously untreated epilepsy, the discontinuation rate due to adverse events was significantly lower among patients on oxcarbazepine (14%) than carbamazepine (26%). Zamponi et al (51) concluded that vigabatrin was found to be well tolerated than carbamazepine in children with newly diagnosed partial seizures, with the most notable adverse effects being irritability, excitability and weight gain. Vigabatrin seems to be effective and safe drug of choice as monotherapy for partial seizures and/or generalized tonic clonic seizures in patients of age 15-64 years with fewer cognitive side effects than carbamazepine (52). Table 2 depicts the side effect profile of newer AEDs. This is not meant to be a comprehensive list but represents the most common adverse effects reported by newer AEDs. The serious adverse effects are mostly life threatening and requires discontinuation of the offending drug. It is therefore recommended to use the specific AEDs in high risk groups with close monitoring. The non serious adverse effects can be easily managed by dosage adjustments.

Drug Interaction Profile of New Versus Old AEDS

Among AEDs, the least interaction potential is associated with gabapentin and levetiracetam whereas lamotrigine and topiramate are most interacting. Among old generation AEDs, carbamazepine, phenytoin, phenobarbital and primidone are hepatic enzyme inducers, causing decreased plasma concentration and reduced pharmacological effect of drugs, which are substrates of the same enzymes (eg; tiagabine, valproic acid, lamotrigine and topiramate). But the

Table 2. Side effect profile of newer AEDs

New AEDs	Serious adverse effects	Non serious adverse effects
Levetiracetam	None	Irritability/behavior change, somnolence, headache
Oxcarbazepine	Hyponatremia (more common in elderly), rash	Dizziness, diplopia, ataxia
Tiagabine	Stupor or spike wave stupor	Weakness, tremor, impaired concentration
Topiramate	Nephrolithiasis, hypohidrosis (mainly in children), open angle glaucoma	Metabolic acidosis, weight loss, language dysfunction
Gabapentin	None	Weight gain, peripheral edema, behavioral changes
Lamotrigine	Rash, Stevens-Johnson Syndrome, toxic epidermal necrolysis (increased risk for children, also more common with concomitant valproate use)	Tics (mainly in children) and insomnia
Zonisamide	Rash, renal calculi, blood dyscrasias, hypohidrosis (mainly in children) Visual field defects, otitis media	Ataxia, irritability, anorexia, fatigue, photosensitivity, weight loss
Vigabatrin	Aplastic anemia, hepatic failure	Sedation, insomnia, dystonia, weight gain
Felbamate		Anorexia, headache, insomnia, gastro intestinal disturbances

new AEDs like gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, vigabatrin and zonisamide do not induce the metabolism of other AEDs (53). Interactions involving enzyme inhibition include the increase in plasma concentrations of lamotrigine and phenobarbital caused by valproic acid. Felbamate, tiagabine, topiramate and zonisamide are sensitive to induction by known enzyme inducing AEDs but are less susceptible to inhibition by common drug inhibitors. These drugs also inhibit CYP2C19 and increase the serum phenytoin concentrations (54).

Lamotrigine when administered concomitantly with carbamazepine and oxcarbazepine can increase the risk of adverse effects like ataxia, diplopia and blurred vision (55). Topiramate can exacerbate valproate associated adverse effects like hypothermia, elevated transaminases and ammonia. Levetiracetam can aggravate the adverse effects of

topiramate mainly in children (56). Co-administration of valproic acid results in the displacement of tiagabine from albumin binding sites and can enhance free pharmacologically active tiagabine levels (57). Valproic acid decreases whereas phenytoin, phenobarbital and primidone increase the rufinamide clearance (58). Rufinamide has no impact on the plasma concentrations of carbamazepine, phenobarbital, primidone, oxcarbazepine, clonazepam or clobazam (59).

Stiripentol inhibits a variety of cytochrome P450 enzymes, resulting in decreased metabolism of such AEDs as phenytoin, carbamazepine and diazepam. Co-administration of carbamazepine, phenytoin, phenobarbital can lead to an increased clearance of a daily stiripentol dose of 1200 mg (18). Stiripentol inhibits the clearance of carbamazepine by 50% and reduces its

transformation to the metabolite carbamazepine 10,11-epoxide (60). It significantly increases the plasma concentrations of clobazam in children with epilepsy (61) and inhibits the hydroxylation of its active metabolite norclobazam (19). Lacosamide does not affect the serum concentrations of carbamazepine, phenytoin, levetiracetam, lamotrigine, topiramate or valproic acid (62). Eslicarbazepine acetate does not affect serum concentrations of carbamazepine, lamotrigine, levetiracetam, topiramate, phenobarbital or diazepam (63). Retigabine does not affect plasma concentrations of carbamazepine, phenytoin, valproic acid, topiramate and phenobarbital (64). It increases the metabolism of lamotrigine (65). Phenytoin and carbamazepine increase the clearance of retigabine. Carbamazepine, oxcarbazepine and phenytoin increase the clearance of perampanel and decrease its plasma concentrations (25). Vigabatrin may enhance the effect of central nervous system depressants (25).

AEDs can interact with other drugs leading to an increase or decrease in the serum concentrations. Valproic acid may increase the plasma levels of zidovudine, lorazepam, nimodipine, paroxetine, amitriptyline, nortriptyline, nitrosureas and etoposide leading to their toxicity (45). Concomitant administration of phenytoin with 5-fluorouracil can lead to increased phenytoin serum levels. Poor seizure control can occur when phenytoin is combined with cisplatin or corticosteroids and valproic acid with methotrexate (66). When valproic acid is added together with carbapenams, it can lead to lower serum valproic acid levels (67). Most of the new generation AEDs are least interacting (68).

Topiramate, felbamate, rufinamide, oxcarbazepine and eslicarbazepine acetate are mild inducers and may affect the disposition of oral contraceptives with a risk of failure of contraception. Estrogen containing oral contraceptives enhance lamotrigine metabolism and decreases its serum levels by more than 50%. Carbamazepine, phenytoin and phenobarbital accelerate the estrogen metabolism and therefore compromise contraception. Enzyme inducing AEDs mainly barbiturates and carbamazepine stimulate the metabolism of warfarin and other coumarin drugs, thereby increasing their dosage requirements (69). Phenytoin may cause an initial increase in anticoagulant effect, however, in the long term, enzyme induction will probably lead to

an increased warfarin metabolism, necessitating increased warfarin doses (70). Valproic acid may increase serum warfarin levels and facilitate bleeding by interfering directly with platelet function and coagulation processes (71). Oxcarbazepine, levetiracetam and tiagabine have not been found to affect the anticoagulant effect of warfarin, but possibility of interaction at higher dosages has not been tested (53). Table 3 lists some of the clinical outcomes of drug interactions involving AEDs.

AEDS Under Development

Brivaracetam, seletracetam, carisbamate, ganaxolone, talampanel, fluorofelbamate and losigamone are the novel AEDs under development.

Brivaracetam, a levetiracetam derivative has been shown to have potent and broad spectrum antiepileptic activity in secondarily generalized motor seizures in corneally kindled mice and clonic convulsions in audiogenic seizure susceptible mice with an efficacy superior to levetiracetam. It is well tolerated and has shown a favorable CNS tolerability profile across doses and without titration. It has shown some efficacy in the treatment of progressive myoclonus epilepsy and is under development to be used as add-on treatment of focal epilepsy (72). Brivaracetam is currently undergoing an intensive clinical assessment in adults with partial onset seizures and as an add-on treatment in adolescents and adults aged 16-65 years with refractory partial onset seizures. It is reported to cause a mere decrease in serum phenytoin levels and carbamazepine area under the curve (AUC) levels (73). It does not modify the steady state plasma concentrations of carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, topiramate or valproic acid (74).

Seletracetam, another levetiracetam analogue does not show anticonvulsant activity in acute seizure models but is effective against hippocampal kindled rats and secondarily generalized motor seizures. It also protects against clonic convulsions in audiogenic seizure prone mice. (75). It is reported to have no clinically significant interactions with other AEDs and also with other drugs (76).

Carisbamate, a neuromodulator with anti-epileptic properties is currently undergoing clinical evaluation of the long term effectiveness, safety and tolerability of the drug as an add-on therapy in

Table 3: Drug interactions involving AEDs

AEDs	Interacting drugs	Mechanism of action	Precautions
Phenytoin	Valproic acid	Displaces phenytoin from plasma proteins, inhibits its metabolism, increased sedative effect	Recommends monitoring of unbound phenytoin concentration
Phenytoin	Topiramate	Decrease phenytoin clearance, increased serum phenytoin levels	If toxicity occurs, reduce phenytoin dose
Phenobarbital	Phenytoin, valproate, carbamazepine	Increases metabolism and reduces serum levels	A higher dose is recommended
Carbamazepine	Valproic acid	1) Inhibition of carbamazepine metabolism, elevated serum levels leading to neurotoxicity 2) Carbamazepine increases valproate metabolism	1) Reduce carbamazepine dose 2) Necessitates a higher valproate dose
Carbamazepine	Lamotrigine	Increases lamotrigine clearance, reduces its serum levels by 34-52%	A higher dose is recommended
Valproic acid	Phenobarbital	Inhibition of Phenobarbital metabolism leading to elevated serum levels	Phenobarbital toxicity; reduce its dose by upto 80%
Valproic acid	Lamotrigine	1) Inhibition of lamotrigine metabolism; increased risk of skin rash 2) A synergistic effect with improved seizure control	Gradual dosage escalation from a low starting dose
Phenytoin	Oxcarbazepine	Reduces phenytoin clearance, increases its serum levels	Closely adjust the AED dosage and monitor
Topiramate	Valproic acid	Inhibits valproate metabolism, exacerbate its adverse effects leading to hyperammonemic encephalopathy	Dosage adjustments and monitoring are needed
Topiramate	Zonisamide	A synergistic effect inducing metabolic acidosis	Recommends low AED dose
Felbamate	Clobazam	Induces clobazam metabolism, lowers its serum concentration	Dosage adjustments are needed
Oxcarbazepine	Lamotrigine	Induces lamotrigine metabolism, reduces its serum levels by 29%	A increased dosage is recommended
Phenobarbital, primidone, phenytoin, lamotrigine	Rufinamide	Increases rufinamide clearance and reduces its plasma levels	Dosage adjustments are necessary

Table 3: Drug interactions involving AEDs.... Continued

Phenobarbital, primidone, phenytoin, carbamazepine	Stiripentol	Induces stiripentol metabolism, lowers its serum concentration	A higher dose is required
Stiripentol	Clobazam	Inhibits clobazam metabolism, increases its plasma levels	Closely monitor for overdose signs
Retigabine	Lamotrigine	Increases lamotrigine metabolism, reduced lamotrigine serum levels	Better seizure control requires an increase in lamotrigine dose
Carbamazepine	Haloperidol, risperidone	Inhibits carbamazepine metabolism, increases its serum levels	Closely monitor for toxicity, adjust dosage
Carbamazepine	Erythromycin, clarithromycin	Inhibits carbamazepine metabolism, precipitates its toxicity	Avoid macrolides that inhibit CYP3A4, use alternatives like azithromycin or spiramycin
Valproic acid	Warfarin	Increases serum warfarin levels and facilitates bleeding	Recommends close monitoring of INR*
Lamotrigine	Oral contraceptives	Induces lamotrigine metabolism, reduces its serum levels by 50%	Close monitoring by increasing lamotrigine dose
Phenobarbital, primidone, phenytoin, carbamazepine, topiramate, lamotrigine, oxcarbazepine	Oral contraceptives	Induction of estrogen metabolism, reduced estrogen levels, therefore compromises contraception	Avoid the use of oral contraceptives >50µg of ethinylestradiol
Phenobarbital, primidone, phenytoin, carbamazepine	Warfarin	Induces warfarin metabolism, reduces its serum levels, increases the risk of coagulation	An increased warfarin dose to maintain INR*
Phenobarbital, primidone, phenytoin, carbamazepine	Cyclosporin, tacrolimus	Induces immunosuppressant metabolism, reduces its serum levels	Increase the immunosuppressant dose
Phenytoin, carbamazepine	Fluoxetine	Elevates serum concentration of the AEDs	Recommends close monitoring of AED dose
Valproic acid	Amitriptyline, nortriptyline	Valproate increases their serum levels by 50-60%	If toxicity occurs, reduce the antidepressant dose

*International Normalized Ratio

patients with partial onset seizures (77). It decreases serum levels of lamotrigine and valproic acid by 20%. Concomitant use of carbamazepine induces the metabolism of carisbamate (78). Carisbamate was also effective in protecting against spontaneous recurrent seizures in kainite treated animals and in genetic models of epilepsy and displayed antiepileptic and neuroprotective activity in the lithium-pilocarpine model of status epilepticus (79). It is tested in patients with post herpetic neuralgia, diabetic peripheral neuropathy and in prevention of migraines.

Ganaxolone does not modify the plasma protein binding of valproic acid (80). In vitro drug-drug interaction studies reported that ganaxolone does not have significant interactions with other AEDs (81). Phenytoin, phenobarbital and carbamazepine have no impact on its interaction profile in children (82). Ganaxolone was found to be safe, effective and well tolerated in refractory infantile spasms with somnolence being the most frequently reported adverse event (83). It was reported to cause a reduction in seizure frequency considered moderate to substantial in 50% of the patients. It is currently undergoing clinical assessment in children with infantile spasms and adults with refractory partial onset seizures (53).

Talampanel is also effective in a mouse model of phenytoin resistant status epilepticus (84). It was found to be well tolerated in refractory partial seizures with dizziness and ataxia were the only significant adverse events (85). Adverse effects occurred at lower doses compared with those in healthy subjects, because of the additive effect of concomitant AEDs. Talampanel increases the plasma concentration of carbamazepine whereas phenytoin and carbamazepine can reduce its plasma concentration.

Fluorofelbamate, a felbamate analogue has been found to have antiepileptogenic properties and reduce the severity of chronic epilepsy after self sustaining status epilepticus (SSSE) (86). It reduced the severity of chronic epilepsy after SSSE and lead to apparent remissions of that epilepsy. Animal studies have investigated that fluorofelbamate reduced the frequency and severity of seizures. It does not cause any behavioral toxicity and give protection against evolution to chronic epilepsy.

Losigamone was found to be an effective add-on therapy for refractory partial seizures for adults (87). In clinical trial, losigamone proved to have satisfactory effectiveness and good tolerance in the

treatment of partial and secondarily generalized seizures. Toxicity studies do not indicate any teratogenic risk of the drug, atleast in animal (88).

CONCLUSION

Selection of most appropriate drug is very crucial in antiepileptic drug therapy. Patients with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, or on the new AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice of AED should be tailored to the characteristics of the individual patient. New AEDs may have some desirable characteristics over the older drugs such as they are as efficacious and better tolerated than standard drugs. However, only a few patients with truly refractory seizures can be made seizure-free by these new drugs, and the search for more effective AEDs should continue. Future studies should be emphasized on the clinical importance of hepatic enzyme induction, changes in clinical response, and long-term side effects to predict their efficacy profile in different patient groups and seizure types. Aligned with an improved understanding of the spectrum of efficacy, mechanism of action, safety and tolerability profiles of AEDs in different age groups, we can foresee an era ensuring the rational use of these drugs.

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