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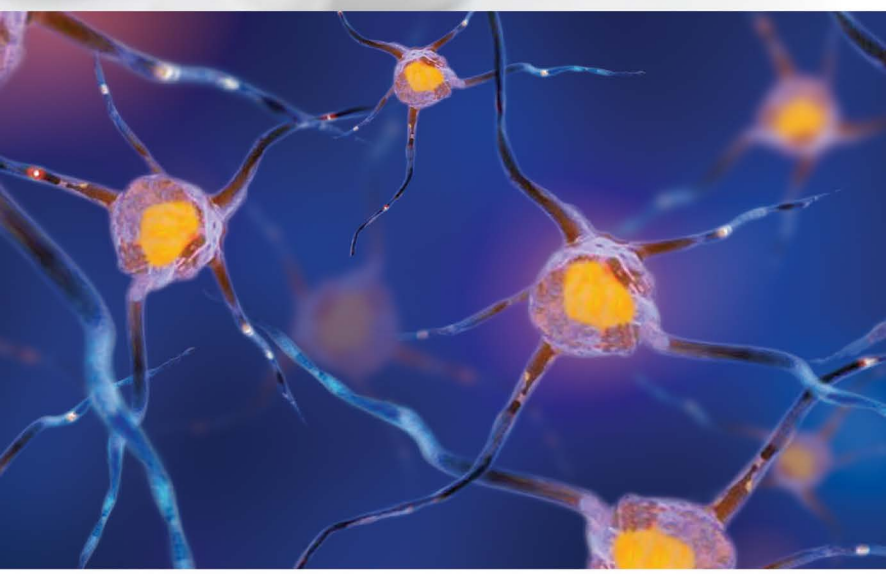

Antiepileptic Drugs

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4
CHAPTER

Newer Antiepileptic Drugs

Neeraj N Baheti

INTRODUCTION

Antiepileptic drug (AED) selection is based on efficacy in the given epilepsy syndrome and patient-specific factors including comorbidities. Over the last two decades, more than 16 newer AEDs acting on different receptors (Table 1) have been approved and marketed. Given such a large number of newer AEDs available, a thorough knowledge of efficacy, pharmacokinetic properties, drug interactions, safety and tolerability profile, and its efficacy against comorbidities is of utmost importance while selecting AED specific to the patient's circumstances. The AEDs are discussed focusing on mechanism of action, pharmacokinetics, drug interactions, approved indications, adverse effects, and dosing and administration. The third-generation AEDs are covered in a separate chapter.

OXCARBAZEPINE

Oxcarbazepine is the 10-keto analog of carbamazepine (CBZ), which blocks high frequency voltage-dependent repetitive neuronal firing of sodium channels (Fig. 1).[1] Oxcarbazepine (OXC) has excellent oral bioavailability and low protein binding. After absorption, it is rapidly converted to monohydroxy derivative (MHD) licarbazepine, which is responsible for antiseizure activity. The half-life of active MHD is 8–10 hours, unlike CBZ no autoinduction is seen on chronic therapy. OXC is metabolized in the liver. It is a weak inducer of CYP3A4 and reduces the efficacy of the oral contraceptive pill at high doses (>900 mg). It is a weak inhibitor of CYP2C19, thus raising the levels of phenytoin (PHT) and phenobarbitone especially when used at high doses.[2]

Indication

Oxcarbazepine is approved as a first-line therapy for focal and secondarily generalized seizures in children and adults. It may

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TABLE 1: Mechanism of action of newer antiepileptic drugs.

Drug	Sodium channels	Calcium channels	Potassium channels	Enhancing GABA	Inhibiting glutamate	SV2A binding	Remarks
Brivaracetam						++	
Clobazam				++			
Gabapentin	+	+		++			
Lacosamide	++						Selective slow voltage-gated sodium channels
Lamotrigine	++	+					
Levetiracetam		+	+	+	+	++	
Oxcarbazepine	++	+	+				
Perampanel					++		Noncompetitive AMPA receptor
Rufinamide	++						
Topiramate	+	+		+	++		Kainate, AMPA and CA receptor antagonist
Zonisamide	+	+					

(+: minor action; ++: major action; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CA: carbonic anhydrase; GABA: gamma aminobutyric acid; SV2A: synaptic vesicle protein 2A)

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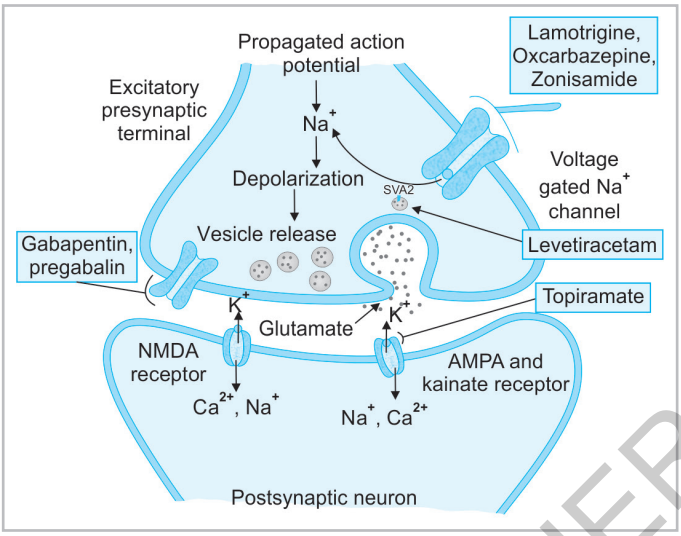

FIG. 1: Mechanism of action of various newer antiepileptic drugs.

exacerbate absence and myoclonic seizures, hence it better avoided in patients with generalized epilepsy.[3,4]

Clinical Implications

Oxcarbazepine with lesser drug interactions, better pharmacokinetics and better safety profile (no epoxy derivative, no autoinduction) is a good alternative first line therapy for focal onset seizures especially in children. It may be particularly useful in patients who respond to CBZ but are unable to tolerate due to adverse effects. However, it is far costlier than CBZ.

Side Effects

Sedation, headache, fatigue, dizziness, blurred vision, diplopia, nausea, vomiting and ataxia are the most commonly reported adverse effects. Rash may occur in 2–4% of individuals. Around 25% of individuals who experience rash with CBZ may also experience it with OXC. OXC is more likely to cause hyponatremia than CBZ especially in older individuals and those taking a diuretic. Very rarely cases of agranulocytosis, aplastic anemia, pancytopenia and thrombocytopenia have been reported with OXC.

Dosage and Administration

Oxcarbazepine is only available as an oral preparation. OXC can be started with initial dose of 300 mg (5–8 mg/kg/day) in two divided doses increasing by 300 mg every week up to a maximum of 1,200 mg twice daily (30 mg/kg/day). Conversion from CBZ can be done overnight; the dose needs to be 1.5 times the CBZ dose.[1]

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LAMOTRIGINE

It acts by blocking the voltage-dependent sodium channels (Fig. 1). There is some evidence that it also inhibits the release of glutamate through stabilization of presynaptic membrane. Lamotrigine (LTG) has an excellent oral bioavailability and it is 55% protein bound. It is metabolized in the liver, predominantly by glucuronidation and then eliminated in the urine. The half-life is about 24 hours in monotherapy. In the presence of valproate, which inhibits glucuronidation the half-life is doubled and drug levels can markedly increase.[5] In the presence of enzyme inducers like CBZ, PHT, rifampicin, the plasma half-life is reduced by half. Combined estrogen-progestin contraceptives decrease LTG levels by increasing clearance conversely; LTG may reduce the effectiveness of combined estrogen-progestin contraceptives.

Dosage and Administration

Lamotrigine is available as an oral preparation only. LTG requires a very slow titration to avoid the development of rash. In monotherapy, start as 25 mg/day for 2 weeks, hike to 50 mg/day for another 2 weeks; thereafter the dose is increased by 50 mg every 1–2 weeks until an optimum response is achieved. The titration rate is half as fast with adjunctive valproic acid, but can be twice as fast in the presence of enzyme inducers.[6] The usual maintenance dose is 200–500 mg and in the presence of concomitant valproate restricted to 100–300 mg. The suggested therapeutic range is 2–20 mg/L. It is also available as extended-release preparation allowing once-daily dosing and also reducing toxicity from peak levels. LTG clearance increases by approximately 65% in pregnancy thus frequent monitoring and dose adjustment is recommended.[7]

Indication

Lamotrigine is approved by FDA for the adjunctive treatment of focal seizures, generalized tonic-clonic seizures and Lennox–Gastaut syndrome (LGS).[4] LTG is a recommended first-line AED for focal seizures and generalized tonic-clonic seizures.[5] Although recommended in generalized absence seizures also but it is less effective than valproate and ethosuximide. It may be effective against myoclonic seizures in some patients, but may exacerbate these seizures in others.[8]

Clinical Implications

Lamotrigine is an effective broad-spectrum AED for the treatment of all types of seizures except myoclonic jerks. In polytherapy, LTG is particularly efficacious with valproate and

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this combination may be ideal for drug-resistant generalized epilepsies including those with myoclonic jerks. Usually, small doses of LTG added to valproate may render previously intractable patients seizure free. In view of mood stabilizing property, it can be a good choice of AED in patients with comorbid mood disorders.

Side Effects

Common dose related side effects include sedation, dizziness, diplopia, ataxia, nausea, vomiting and tremors. Serious side effects of LTG often requiring drug withdrawals include skin rash and rarely Steven–Johnson syndrome and toxic epidermal necrolysis. The risk of rash increases when LTG is administered with valproate or when the dose is titrated rapidly.[9]

■ TOPIRAMATE

Topiramate (TPM) has multiple mechanisms of action. It enhances gamma-aminobutyric acid (GABA) mediated inhibition, blocks voltage-dependent sodium channels and L-type voltage-activated calcium channels and antagonizes N-methyl-D-aspartate (NMDA)-glutamate receptor (Fig. 1). It is also a weak inhibitor of carbonic anhydrase. TPM has an excellent oral bioavailability (>80%). Its protein binding is not clinically significant. It is partially metabolized in the liver and about 70% is eliminated unchanged in the urine. Its half-life is approximately 20–30 hours when used as monotherapy. Enzyme-inducing AEDs can reduce plasma levels of TPM by nearly half by increasing clearance. Conversely, TPM can reduce PHT clearance thus increasing blood levels. TPM may reduce the effectiveness of hormonal contraceptives.[2]

Dosage and Administration

Topiramate is available as oral preparation only. TPM is initiated at 25 mg twice daily, the dose can be increased by 25–50 mg every week. The dose can be hiked up to 200–400 mg/day and in the presence of enzyme-inducing AEDs, the dose can be hiked up to 600 mg/day.

Indication

Topiramate is a broad-spectrum AED. TPM is approved as monotherapy or adjunctive therapy for focal and generalized tonic-clonic seizures in patients 2 years and elders.[4] It is approved for adjunctive treatment of seizures associated with LGS.[10] Although approved, TPM is usually not preferred as first line because of its cognitive adverse effects, unless its use is justified by comorbidity such as migraine or obesity.[11]

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Clinical Implications

Topiramate is a broad-spectrum AED useful in as adjuvant therapy in resistant focal and symptomatic generalized epilepsies. It can be preferred as initial monotherapy in obese or with concomitant migraine.

Side Effects

Common adverse effects include psychomotor slowing, decreased attention, executive dysfunction, impairment of language, word-finding difficulty, reduced verbal fluency and slurred speech. Other side effects include sedation, fatigue, dizziness, ataxia and depression. In children, hypohydrosis, hyperthermia and metabolic acidosis are rare serious side effects. Acute myopia, secondary angle glaucoma and renal stones have also been reported. Weight loss is a common dose-related side effect. Paresthesia of hands and feet is another commonly reported adverse effect probably related to carbonic anhydrase inhibition. Hyperammonemia may occur, especially, if used in conjunction with valproate.[12]

■ CLOBAZAM

Clobazam is 1,5-benzodiazepine, enhances the inhibitory effects of GABA. It binds to the GABA-A receptor and increases the frequency of GABA-mediated chloride channel openings.[13] Clobazam has good oral bioavailability and is highly protein bound (85%). Clobazam is metabolized in the liver to the active N-desmethylclobazam. Elimination half-life in adults is 10–30 hours, justifying once daily dosing. Dose adjustments are required in patients with hepatic insufficiency. Enzyme-inducing AEDs can increase plasma clearance of clobazam and decrease serum levels.

Dosage and Administration

Clobazam is available as oral preparation only. Clobazam is usually initiated at 5 mg/day in one dose, typically given at bedtime. The dose may be increased every 1–2 weeks to a maximum of 40 mg/day. Unlike other benzodiazepines, clobazam has least propensity for tolerance.

Indication

Clobazam is a broad spectrum AED used as an adjunctive therapy in focal and generalized tonic-clonic seizures especially in drug-resistant epilepsy scenarios. In United States, clobazam is recently approved as an adjunctive therapy in LGS.[14]

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Clinical Implications

Clobazam is a broad spectrum, good adjunctive medication useful in all drug-resistant epilepsies. It has a lower propensity for tolerance and drug dependence compared to other benzodiazepines. It is a very good add-on drug for focal epilepsy and can be used for long-term.

Side Effects

Adverse effects include somnolence and sedation, dysarthria, drooling, aggression or other behavioral changes. Withdrawal seizures may occur with abrupt discontinuation.

■ LEVETIRACETAM

Levetiracetam (LEV) acts by novel mechanisms by inhibiting the synaptic vesicle protein SV2A, an integral membrane glycoprotein involved in synaptic vesicle exocytosis (Fig. 1).[15] There is also evidence that LEV indirectly modulates GABA and glycine gated currents, and can partially inhibit N-type calcium.[16] LEV has an excellent oral bioavailability (95%) and very low protein binding. It has no hepatic metabolism; 66% is excreted unchanged in the urine and the rest is hydrolyzed to inactive compounds. The half-life is 6–8 hours in adults. It has no known significant pharmacokinetic interactions.

Indications

Levetiracetam is a broad-spectrum drug, approved as an adjunctive therapy for focal onset seizures, generalized tonic-clonic seizures, and generalized myoclonic seizures.[4] Intravenous preparation has shown efficacy in acute seizures and status epilepticus.

Clinical Implications

Levetiracetam is a broad-spectrum drug with a favorable pharmacokinetic profile in terms of safety and absence of any interactions with other AEDs or concomitant medications. It is a first line contender for idiopathic generalized epilepsy where it is replacing valproate and in focal seizures where it is a main challenger for CBZ, especially in child-bearing age group females.

Adverse Effects

Levetiracetam is usually well tolerated. The most common adverse effects include headache, dizziness, asthenia and somnolence. A reversible thrombocytopenia is seen in a small

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number of patients. However, there are concerns of behavioral side effects like aggression, emotional labiality, oppositional behavior and psychosis especially in children or those who are intellectually disabled and have baseline behavioral problems.[17,18]

Dosage and Administration

Levetiracetam is available in oral and intravenous formulations. Initiate levetiracetam as 500 mg (10 mg/kg/day) in two divided doses. The dose can be hiked every 2 weeks as needed for seizure control. Usual maintenance dose is 2,000–3,000 mg/day; some patients may tolerate and respond to doses as high as 4,000 mg/day. In children usual maintenance dose is 30–40 mg/kg; doses up to 60 mg/kg/day may be needed and well tolerated by younger children.

■ ZONISAMIDE

Zonisamide is structurally a sulfonamide derivative, which has multiple mechanisms of action. It acts by blocking sodium channels, T-type calcium channels and carbonic anhydrase inhibition (Fig. 1). Zonisamide has excellent oral bioavailability (>90%) and low protein binding (40%). It is metabolized primarily in the liver and excreted through kidney. It has a long half-life of around 60 hours. It is not recommended in patients with severe hepatic or renal impairment. It is not an enzyme inducer or inhibitor but its clearance may be increased when used enzyme-inducing AEDs like CBZ, PHT or phenobarbital.

Indication

Zonisamide is a broad-spectrum agent approved as an adjuvant therapy for focal seizures in adults and children.[19,20] It has also been approved as monotherapy for focal seizures in Europe and generalized epilepsy in Japan.

Clinical Implications

Zonisamide is an effective broad-spectrum AED useful as an adjunctive therapy in drug-resistant epilepsy and epileptic encephalopathies. It is quite effective in myoclonic jerks and hence can be used is idiopathic generalized epilepsies.

Dosage and Administration

The starting dose is 100–200 mg/day for 2 weeks. Because of its long half-life, once-a-day dosing is often effective. The dose can be increased by 100 mg every 2 weeks up to 600 mg/day as needed for seizure control.

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Side Effects

Most common adverse effects include somnolence, ataxia, anorexia, weight loss and agitation or irritability. Other rare side effects include severe skin rash like Stevens–Johnson syndrome or toxic epidermal necrolyisis. It can lead to oligohydrosis, hyperthermia and nephrolithiasis especially in children. Cognitive slowing and difficulty with concentration may be seen, particularly at higher doses.

■ GABAPENTIN

Gabapentin binds to the α2-δ subunit of voltage-gated calcium channels, reducing the influx of calcium and associated neurotransmitter release, thus in turn decreasing excitablity (Fig. 1).[21] Gabapentin is absorbed by means of saturable amino acid transport systems in the gut and the bioavailability of gabapentin is low (<60%). The drug does not bind to plasma protein, nor is it metabolized. It is eliminated unchanged in the urine. Its half-life is 5–7 hours. It has no known interactions, other than potential antacid interference with its absorption.[22]

Dosage and Administration

The recommended starting dose of gabapentin is 300–400 mg/day, increased by 300–400 mg every day up to 300–400 mg three times a day. The dose can be increased as needed up to 3,600 mg/day in three divided doses. The antiseizure effects of gabapentin are dose related, and the therapeutic effects of doses less than 900 mg/day may be small.

Indication

Gabapentin is approved as monotherapy or adjunctive therapy for focal seizures with or without secondary generalization.[4] Although approved in Europe for initial monotherapy, a large randomized comparative trial found it less effective than LTG.[5]

Clinical Implications

Gabapentin appears to be a narrow-spectrum AED whose role in the management of partial seizures is limited because its efficacy is weak compared with other AEDs.

Side Effects

The common adverse effects include drowsiness, dizziness, ataxia, tiredness and weight gain. It may cause cognitive slowing in the elderly and emotional labiality in children.

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PREGABALIN

Pregabalin modulates α2-δ protein subunit of voltage-gated calcium channels reducing calcium influx and excitability (Fig. 1).[21]

It does not bind to plasma proteins. The elimination half-life is 5–7 hours, it is excreted unchanged in urine. It has no significant interactions with other drugs.

Dosage and Administration

The starting dose is 75 mg once (at bedtime) or twice daily. The dose can be increased by 75 mg every week as needed, until seizure control, appearance of adverse effects, or reaching a maximum dose of 300 mg two times a day.

Indication

Pregabalin is a narrow-spectrum drug against focal seizures. The official FDA epilepsy indication is adjunctive therapy for adult patients with focal onset seizures.[4] Pregabalin may exacerbate generalized myoclonic and absence seizures.[23]

Clinical Implications

Although approved as adjunctive therapy, the role of pregabalin in management of partial seizures is not fully ascertained. It is reserved for intractable partial seizures who have failed to respond to other AED combinations.

Side Effects

The most common side effects include dizziness, somnolence, increased appetite, weight gain and peripheral edema.

CONCLUSION

Many newer and safer AEDs are available for the treatment of epilepsy. The knowledge of pharmacokinetics, efficacy and tolerability profiles facilitates the choice of appropriate antiepileptic medication for patients with epilepsy.

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Antiepileptic Drugs

Key Features

- This book is a comprehensive resource providing clinical and up-to-date information on effective selection and usage of antiepileptic drugs
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