New antiepileptic drugs

A clinical overview

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ABSTRACT

After a gap of approximately 20 years, a new generation of antiepileptic drugs (AEDs) has recently been developed. More than 8 drugs have been licensed in at least one country during the 1990s. While lamotrigine, gabapentin, vigabatrin and oxcarbazepine are widely used in some countries, felbamate, topiramate, tiagabine, levetiracetam, and zonisamide are still used on a narrow scale. A feeling of optimism occurs after the development of these drugs, although only a small number of epileptic patients become free of seizures after the addition of these new AEDs to their regimen. Generally, the safety profile of the new AEDs is only slightly better than that of established drugs and their efficacy is strongly associated with the use of high doses. This article reviews new AEDs by studying their clinical pharmacological effects, mechanisms of action as antiepileptic agents, side effects, drug-drug interactions and the appropriate regimen of their use.

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Epilepsy remains poorly understood despite half a century of intensive investigation. Medical statistics show that epilepsy is the second most common neurological disorder after stroke. Medical treatment of epilepsy has improved to the point that approximately 75% of people diagnosed can have their seizures either reduced or entirely eliminated.[1] The most commonly prescribed form of treatment is daily medications. Effective treatment depends largely on the physician's ability to establish an accurate diagnosis and choose appropriate therapy based on the likelihood of clinical benefit as well as potential side effects. After the development of a new generation of antiepileptic drugs, clinicians started using these drugs as a monotherapy or as an add-on therapy. This review is designed to provide clinical information about these new antiepileptic drugs in a simple but comprehensive way in relation to their use in epilepsy without overwhelming the reader with pure basic data.

Therapeutic options. There are several properties that are desirable in an AED. The agent should have a mechanism of action that provides a rational basis to control seizure activity when used alone or in combination with other AEDs. Also, there should be an increased tolerability and therapeutic index, such that dose-limiting toxicity and side effects, as seen with traditional AEDs will not be problematic. Lack of teratogenic potential is also desirable, since the care of females of childbearing age and during pregnancy is often challenging and requires further risk-versus-benefit considerations. Pharmaceutical properties, including multiple dosage formulations. Pharmacokinetic profiles that are simple and do not cause many drug interactions are desirable for

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dosing and administration purposes. A summary of desirable AED properties, the mechanisms of action, efficacy, maintenance doses, drug interactions and common and serious adverse effects are summarized in **Tables 1-5**. The new AEDs that have recently been approved are a result of considerable research and development to overcome the problems and disadvantages of traditional AEDs.

Lamotrigine (Lamictal, LTG). Lamotrigine is useful as adjunctive therapy in both children and adults. It is also being used as monotherapy especially in patients not responding to the first line drugs. This drug was developed because it has an antifolic activity which was thought could block epileptic activity. However, the drug produces its antiepileptic effect by blocking voltage-dependent sodium channels, thus stabilizing presynaptic neuronal membranes and preventing the release of excitatory glutamate and aspartate.[2] After oral administration, LTG is well absorbed and 55% is bound to plasma protein. It has linear kinetics with an elimination half-life of approximately 25 hours. The liver extensively metabolizes it. The drug does not affect the metabolism of other AEDs, warfarin or oral contraceptive pills. Hepatic enzyme inducers such as phenobarbital, phenytoin and carbamazepine reduce LTG's half-life (to approximately 15 hours) and thus, higher doses are required when used concomitantly. On the other hand, hepatic enzyme inhibitors such as sodium valproate prolong its half-life (to approximately 60 hours), thus reduced doses are required if both drugs are used together. A pharmacodynamic interaction also exists between LTG and the 2 old antiepileptic drugs; valproate and carbamazepine. An LTG-valproate combination aggravates the tremor of valproate and LTG-carbamazepine combination aggravates the central nervous systems (CNS) adverse effects of carbamazepine.[3]

Lamotrigine is used in partial seizures with or without secondary generalization. It is used in tonic–clonic seizures as a first–line drug, and in refractory epilepsy as a second–line drug. Moreover, this drug was shown to be effective in primary generalized epilepsy including atonic, typical, atypical absences and myoclonic jerks.[4] Tolerance has not been observed to its anticonvulsant action. In children, LTG has the same efficacy in controlling seizures as in adults and is particularly beneficial in children with infantile spasm and Lennox-Gastaut syndrome.[5] When combined with sodium valproate, LTG has an enhanced efficacy in the management of generalized absence, myoclonic seizure or both. Additionally, when combined with vigabatrin, it has an increased efficacy in patients with partial seizures.[2]

The dose of LTG is 5/mg/kg/day when used with sodium valproate, 10/mg/kg/day when used alone and 15/mg/kg/day when used with an enzyme inducer. The treatment should be titrated upward slowly over several weeks to reduce the incidence of adverse reactions especially skin rash, until reaching a maximum dose of 400 mg/day in 2 divided doses.[4] A drug concentration range of 1-4 mg/l was chosen arbitrarily for a clinical trial program, however, no clear correlation between plasma LTG levels and its efficacy or toxicity has been established. In addition to its use in epilepsy, clinical reports indicate that LTG is a useful drug in the treatment of trigeminal neuralgia secondary to multiple sclerosis[6] and in patients with bipolar disorders.[7]

The most common side effects of LTG are headache, dizziness, ataxia and diplopia. Sedation rarely occurs. Skin rash is the most common idiosyncratic adverse effect and occurs in 3-5% during the initial management with a higher incidence in those with higher initial dose and those taking sodium valproate concomitantly. The rash may subside spontaneously in mild cases without requiring drug withdrawal, however in some patients systemic symptoms may develop as malaise, arthralgia, myalgia, lymphadenopathy and eosinophilia.[8] Bullous erythema multiforme, Steven's-Johnson and Lyell's syndromes have been reported in less than 1% of the cases. Few fatalities due to disseminated intravascular coagulopathy and fulminant hepatic failure have been recorded. Moreover, clinical reports indicate that LTG can induce a systemic lupus erythematosus-like picture.[9] No evidence of teratogenicity has been reported.

Vigabatrin (Sabril, VGT). This drug increases the level of gamma-aminobutyric acid (GABA) by an irreversible inhibition of GABA transaminase, the enzyme that degrades GABA. This effect is proposed to be the mechanism of its antiepileptic activity.[10] The drug is rapidly absorbed after oral administration with minimal plasma protein binding and is excreted unchanged by the kidneys. Its short half-life (5-7 hours) is not related to its duration of action that exceeds 24 hours, therefore, monitoring the plasma concentration of VGT can not be used to predict the clinical response.[11] Vigabatrin has no known drug interaction other than a reduction in plasma concentration of phenytoin by 25% probably by decreasing its absorption. However, this interaction has no clinical significance.[12]

Vigabatrin is used as a second-line treatment in patients with resistant partial seizures with or without secondary generalization and as a first-line treatment in infantile spasm (West's syndrome).[13] It is also effective as a monotherapy in newly diagnosed adults with partial onset seizures and tonic-clonic seizures. The drug can worsen myoclonic jerks and generalized absence and precipitate status epilepticus. Tolerance to its antiepileptic activity may develop in one third of the

Table 1 - Possible mechanisms of action of new AEDs.

AED	Mechanism of action
LTG	Blocking voltage-dependent sodium channels and decreasing the release of excitatory neurotransmitters
VGT	Irreversible inhibition of GABA transaminase
GBP	Inhibition of voltage-dependent sodium or calcium channels or binding to specific receptors
FBM	Inhibition of NMDA receptors or potentiating of GABA
TOP	Inhibition of sodium channels, inactivating kainate/ AMPA receptors or potentiating GABA
OXC	Inhibit voltage-dependent sodium or calcium channels
ZNS	Inhibit voltage-dependent sodium channels or T-Type calcium channel
TGB	Inhibit reuptake of GABA into neurons and glial cells
LVT	Not established yet

LTG - Lamotrigine, VGT - Vigabatrin, GBP - Gabapentin, FBM - Felbamate, TOP - Topiramate, OXC - Oxcarbazepine, ZNS - Zonisamide, TGB - Tiagabine, LVT - Levetiracetam GABA - gamma-aminobutyric acid, NMDA - N-methyl-D-aspartate, AEDs - antiepileptic drugs

Table 3 - Efficacy of new AEDs against different types of seizures.

Partial/ Secondarily generalized	Tonic-clonic	Absence	Myoclonic	LGS	Infantile spasm
LTG	LTG	LTG	LTG	LTG	LTG(?)
VGT	ZNS	FBM(?)	TOP	FBM	VGT
GBP	TOP			VGT(?)*	TOP
FBM	OXC			TOP	
OXC	VGT(?)				
TOP	FBM				
TGB	LVT				
ZNS					
LVT					

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LGS - Lennox-Gastaut syndrome, (?) - may be effective, *VGT - may make myoclonic seizure in LGS worse

Table 2 - Drug interaction of new AEDs.

Added AED	PB	PHT	CBZ	VPA	ESM
LTG	N	N	N	N	N
VGT	↓	↓	N	N	N
GBP	N	N	N	N	N
FBM	?	↑	↓	↑	?
OXC	↓	↓	↓	↓	↓
ZNS	↓	↓	↑	↓	?
LVT	↓	↓	↓	↓	↓

	LTG	VGT	GBP	FBM	OXC	ZNS
PB	↓	N	N	↓	↓	↓
PHT	↓	N	N	↓	↓	↓
CBZ	↓	N	N	↓	↓	↓
VPA	↑	N	N	N	N	?
ESM	N	N	N	?	?	?
LVT	↓	↓	↓	↓	↓	↓

LTG - Lamotrigine, VGT - Vigabatrin, GBP - Gabapentin, FBM - Felbamate, OXC - Oxcarbazepine, ZNS - Zonisamide, LVT - Levetiracetam, PB - Phenobarbital, PHT - Phenytoin, CBZ - Carbamazepine, VPA - Valproate, ESM - Ethosuximide, N - no interaction, ↑ - increased level, ↓ − decreased level, ? - not enough data AEDs - antiepileptic drugs

Table 4 - Maintenance doses of new AEDs.

AED	Dosage Form	Adults (mg)	Children
LTG	Tablets 25, 50, 100, 200 mg Dispersible Tablets 5 mg	A. 200 B. 500 C. 800	A. 5 (mg/kg/day) B. 10 (mg/kg/day) C. 15 (mg/kg/day)
VGT	Tablets 500 mg Powder 500 mg/sachet	2000-3000	80-100 (mg/kg/day)
GBP	Capsule 100, 300, 400 mg Tablets 600, 800 mg	1200-2400	900 mg (Weight 26-36 Kg)†
FBM	Tablets 400, 600 mg Oral Suspension 600 mg/5ml	1800-4800	30-45 (mg/kg/day)
TOP	Tablets 25, 50, 100, 200 mg Sprinkle Cap 15, 25, 50 mg	200-1000	3-10 (mg/kg/day)
OXC	Tablets 150, 300, 600 mg Oral Suspension 300 mg/5ml	900-2400	10-30 (mg/kg/day)
ZNS	Two-piece hard gelatin Capsule, 100 mg	200-500	N
TGB	Tablets 5, 10, 15 mg	30-60	*
LVT	Tablets 250, 500, 1000 mg	1000-3000	*

LTG - Lamotrigine, VGT - Vigabatrin, GBP - Gabapentin, FBM - Felbamate, TOP - Topiramate, OXC - Oxcarbazepine, ZNS - Zonisamide, TGB - Tiagabine, LVT - Levetiracetam, AEDs - antiepileptic drugs,
A - when LTG is used with valproate
B - when LGS is used as monotherapy
C - when LTG is used with enzyme inducer
* - not recommended in children under 12 years
N - not enough data
† - based on the British National Formulary (BNF) March, 2003

Table 5 - Common adverse effects of new AEDs.

AED	Adverse effects
LTG	Headache, dizziness, rash, *erythema multiforme, *Steven-Johnson syndrome
VGT	Sedation, weight gain, *depression, *psychosis, *retinal toxicity
GBP	Drowsiness, dizziness, ataxia, gastrointestinal upset
FBM	Headache, nausea, vomiting, weight loss, anorexia, insomnia, *aplastic anemia, * hepatotoxicity
TOP	Confusion, slurred speech, fatigue, sedation, *renal stones, *weight loss, *metabolic acidosis
OXC	Diplopia, headache, dizziness, vomiting, ataxia
ZNS	Sedation, headache, dizziness, *renal stone
TGB	Dizziness, sedation, confusion
LVT	Sedation, fatigue, incoordination, psychosis

LTG - Lamotrigine, VGT - Vigabatrin, GBP - Gabapentin, FBM - Felbamate, TOP - Topiramate, OXC - Oxcarbazepine, ZNS - Zonisamide, TGB - Tiagabine, LVT - Levetiracetam, AED - antiepileptic drug, *serious adverse effect

cases. Treatment is started with small doses of 250-500 mg/day and increased slowly over several weeks to allow tolerance to sedation induced by the drug. If the patient developed agitation or thought disorder, the drug should be withdrawn. Most patients have their best response at 2-3 gm daily, and the dose should be less in patients with creatinine clearance less than 35 ml/min. In this case, the dose should be tapered off over 3-4 weeks otherwise increased seizures and even psychosis can occur.[14] In children, the initial dose is 50 mg/kg/day with a gradual increase according to response up to 80-100 mg/kg/daily. Patients with infantile spasm may require up to 100 mg/kg/day or even more. Central nervous system effects (sedation, dizziness and headache) are the most common adverse effects particularly when the dose is high, these symptoms are frequently self-limiting. Change in mood, agitation, ill-temper and disturbed behavior may develop in 10% of the patients. This drug should not be prescribed in patients with a history of behavioral disturbances or severe depression.[15] Visual function deficits of the central retina have been identified in approximately 20-40% of patients receiving VGT.[16] Vigabatrin associated retinal toxicity is diffuse inducing subtle central visual dysfunction and more severe peripheral visual defects.[17] It can be asymptomatic and irreversible. This requires a clinical examination by perimetry and electroretinogram (ERG) to screen for this adverse event.[16] Cognitive impairment does not occur but weight gain has been reported. This drug is teratogenic in animal models manifested as an increase in the incidence of fetal cleft palate and so its use in pregnancy is not recommended.[12]

Gabapentin (Neurontin, GBP). This drug is an amino acid,[18] a GABA analogue that was shown to be inactive at GABA receptors. Its mechanism of action is unclear, however, it is postulated that its antiepileptic activity may be related to inhibition of sodium channels, calcium channels or binding to specific receptors in the brain.[19] Gabapentin is rapidly absorbed from the gastrointestinal tract via the amino acid transport system. It is not metabolized by the liver, not bound to plasma protein and is excreted unchanged by the kidneys with an elimination half-life of 5-7 hours. No clinically important interactions with other drugs have been reported to date. It does not affect hepatic enzymes and does not affect the plasma concentration of other AEDs; warfarin and oral contraceptive pills This characteristic gives the drug an advantage when drug interaction is a troublesome. Its renal elimination is reduced by 12% if given with cimetidine.[20]

Gabapentin is used as a second-line therapy of partial seizures with or without secondary generalization and in tonic-clonic seizures. No tolerance to its antiepileptic effect has been reported. In adult patients with monotherapy, the initial dose is 300 mg/day with a daily increment increase of 300 mg reaching a dose of 1200-2400 mg/day in refractory epilepsy. In polytherapy, a slower titration is required with a weekly increase of 300 mg. The drug should be given thrice daily in most patients due to its short half-life, and the dose should be reduced in patients with renal impairment.[21] Plasma concentration measurement is unnecessary because it has a short elimination half-life with a wide therapeutic ratio. Recent clinical reports indicate that GBP can be a potential agent in the treatment of chronic pain in spinal cord injury,[22] cluster headache,[23] painful peripheral neuropathy, and acute mania.[24] This drug is well tolerated with drowsiness being the most frequent side effects. Other adverse effects include sedation, fatigue, ataxia, tremor, dizziness, gastrointestinal upset and weight gain. It has not been associated with idiosyncratic reactions or teratogenic effects.[25]

Felbamate (Felbatol, FBM). This drug is related structurally but not functionally to the anxiolytic meprobamate. It was licensed in the USA in 1993 for the treatment of refractory epilepsy in adults and Lennox-Gastaut syndrome in children, but the appearance of aplastic anemia and hepatotoxicity limits its use. The exact mechanism of its action in epilepsy is not clear, but it may produce its antiepileptic activity by inhibitory action on voltage-dependent sodium channels, potentiating GABA response at the GABA receptor, as well as, inhibition of the excitatory N-methyl-D-aspartate

(NMDA) receptors and potentiation of the inhibitory GABA response.[26]

The drug is rapidly absorbed from the gastrointestinal tract with plasma protein binding of 22-36% and it undergoes hepatic metabolism with an elimination half-life of 15-23 hours. Felbamate increases the plasma concentrations of phenytoin by 20% and of sodium valproate by 50% and reduces the plasma carbamazepine concentration by 20-25% but with an increase of its metabolite 10,11-epoxy–carbazepine.[20] While enzyme-inducing AEDs particularly carbamazepine and phenytoin reduce the half-life and plasma concentration of FBM, liver enzyme inhibitors such as valproate increases its level. The drug decreases the effect of concomitant low dose oral contraceptive pills which, is manifested clinically as break through bleeding.[27]

Felbamate has a broad spectrum of action, but due to its serious adverse effects, it is now recommended as a last resort for patients with refractory epilepsy particularly those with Lennox-Gastaut syndrome. The risks of the drug should be explained to the patients and consent to treatment should be obtained. The recommended initial dose is 400 mg/day with weekly upward titration of 400 mg/day up to 1200 mg/day in 2-3 divided doses, then an increase by 600 mg/day each week until seizure control is achieved or adverse effects develop. Maintenance dose range is from 1800-4800 mg/day. It is recommended to have a weekly, or a biweekly complete blood count and liver function tests in addition to a base-line measurement prior to initiation of FBM therapy. In children with Lennox-Gastaut syndrome or between the age of 2-14 years, the initial dose is 15 mg/kg/day and the maintenance dose is 30-45 mg/kg/day in 3 or 4 doses.[28]

Adverse effects occur in half of patients receiving FBM, most commonly neurological (insomnia, headache, dizziness, diplopia and ataxia) and gastrointestinal (anorexia, nausea and vomiting). Weight loss was also reported. The major problem is the development of aplastic anemia and hepatotoxicity that could be fatal. Recently, the use of FBM and VGT in children is limited because of specific idiosyncratic adverse effects.[16] The incidence of these adverse effects being one in 3600-5000 for FBM and one in 24000-34000 for VGT.[29]

Topiramate (Topamax, TOP). Topiramate is used as an adjunctive for partial and generalized seizures in adults and children (more than 2 years of age). It is also useful as adjunctive therapy in the treatment of Lennox-Gastaut syndrome and infantile spasm. This drug is a sulfurated fructose which has a weak inhibitory action to carbonic anhydrase not related to its antiepileptic activity. Its mechanism of action is believed to involve blocking of sodium channels, inactivating the kainate/AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propionic acid-type glutamate receptors or increasing the inhibitory action of GABA by acting on a unique modulatory position.[30] It has linear pharmacokinetics with low plasma protein binding and a half-life of approximately 21 hours. Its elimination is decreased in severe renal or hepatic diseases. In some patients, TOP reduces the plasma clearance of phenytoin aggravating its toxicity. In addition, it reduces ethinylestradiol concentration in women receiving oral combined contraceptive pills. Hepatic enzyme-inducers AEDs reduce TOP concentration by increasing its metabolism.[12,31]

Topiramate is used as a second-line drug in patients with partial seizures with or without secondary generalization, especially refractory ones. It can also be used in primary generalized tonic-clonic seizures and in patients with Lennox-Gastaut syndrome. Tolerance to its anticonvulsant effect is not evident, yet.[30] Monitoring TOP's concentration is not needed during routine treatment. An initial dose of 25 mg once daily is advised with an increase of 25 mg/day every 2 weeks up to 200 mg/day, then 50 mg/day each week until control of seizures is achieved or side effects develop. A dose of 200-600 mg/day is usually recommended although some patients require higher (up to 1000 mg) doses to control their seizures. The dose in children is 3-10 mg/kg/day.

The most adverse effects are CNS related and usually transient. Those include: confusion, ataxia, slurred speech, dizziness, poor concentration, fatigue, sedation and cognitive impairment. Moreover, weight loss, taste disorders, visual disorders and psychotic symptoms have been reported.[15] The inhibition of carbonic anhydrase enzyme by TOP may be responsible for the development of paresthesia and nephrolithiasis in 1-2% of patients taking this drug. The development of nephrolithiasis is increased in patients who use TOP and have a history of renal stones, receiving calcium or vitamin C supplements.[32] Patients taking TOP should be advised to increase fluid intake in order to reduce the risk of stone formation. In animal studies, high doses of TOP were teratogenic, so it is best avoided in pregnancy.

Oxcarbazepine (Trileptal, OXC). This drug is a 10-keto analogue of carbamazepine. One-third of the patients who are hypersensitive to carbamazepine have cross sensitively to OXC. Its mechanism of action is similar to carbamazepine, which involves blocking of voltage-dependent sodium channels. Oxcarbazepine is a pro-drug that is converted rapidly in the liver to the active moiety 10-11dihydro-10-hydroxy carbamazepine.[33] It has a 40% plasma protein binding and eliminated mostly by the kidney with a half-life of 8-10 hours. This drug has less autoinduction properties than

carbamazepine. Unlike carbamazepine, it does not affect the metabolism of other AEDs and has no inhibitory interaction with dextropropoxyphene and erythromycin, which is observed with the use of carbamazepine. However, it reduces the levels of ethinylestradiol and levonorgestrel, which may reduce their efficacy as contraceptive agents.[34]

Oxcarbazepine has similar efficacy and indications to its parent drug carbamazepine. It has fewer side effects than carbamazepine and phenytoin with equal efficacy and is used in patients older than 4 years of age. It is used successfully in partial seizures with or without secondary generalization. Similar to carbamazepine, it has no effect and may worsen absences and myoclonic seizures.[35] Studies suggest that the drug has the same efficacy in children compared with adults. An initial dose of 300 mg/day is indicated with an increase of 300 mg/day weekly reaching a daily dose of 900-2400 mg in 3 divided doses. In children over 3 years, an initial dose of 10 mg/kg/day is recommended, increased gradually to approximately 30 mg/kg/day as a maintenance dose. Clinical reports indicate that OXC may be used in the treatment of trigeminal neuralgia and affective disorders.[36]

Adverse effects of OXC are less than carbamazepine and mostly related to the CNS. Those include: drowsiness, dizziness, headache, diplopia, nausea, vomiting, and ataxia.[37] Allergic skin rash is less common than carbamazepine but hyponatremia secondary to the increase in the production of ADH is asymptomatic in most patients. Hepatotoxicity and blood dyscrasia are not noticed with the use of OXC. Although teratogenic in animal models, there is no evidence for this effect in humans.[38]

Zonisamide (Zonegran, ZNS). This drug is a sulfonamide analogue with unknown mechanism of action in the treatment of epilepsy. However, blocking of sodium channels or T-type calcium channels was proposed.[39] It is well absorbed orally with a long half-life (55-68 hours) allowing once daily dosing. It is less than 50% protein bound and undergoes liver metabolism. This drug is used as a second-line treatment for patients with partial seizure with or without secondary generalization. It is also used in tonic-clonic seizures. Recommended doses are between 200-500 mg/day, although some patients may require doses outside this range. The recommended initial dose for most patients is 100 mg once daily, titrating upward every 2 weeks in 100 mg/day incremental steps until seizure control is achieved or side effects develop.[40]

Zonisamide does not effect the levels of carbamazepine, barbiturates or valproate, but increases the plasma concentration of phenytoin by approximately 10-15%. Liver enzyme inducer AEDs increase the metabolism of ZNS. Based on this, higher ZNS doses may be necessary during co-administration with these AEDs.[41] Side effects of ZNS are mostly CNS related. They include dizziness, drowsiness, headaches, sedation and anorexia. Other side effects include: nausea and vomiting, weight loss, skin rashes, irritability, impaired concentration and fatigue. Although rare (0.2-1.9%), the main limiting factor in its use is the development of renal stones.[42] Zonisamide is contraindicated in patients with allergies to sulfonamides or related sulfa drugs. This drug should be used with caution in patients with hepatic and renal impairment since it is eliminated by the liver and kidneys.

Tiagabine (Gabitril, TGB). This drug produces its antiepileptic action by increasing the availability of GABA in the CNS. Tiagabine is indicated as adjunctive treatment in partial and secondarily generalized seizures. This mechanism is achieved by inhibition of GABA reuptake in neurons and glial cells by binding to a GABA transporter known as GAT-1.[43] It is rapidly absorbed after oral administration with bioavailability that approaches 100% and half-life of 5-9 hours. It undergoes hepatic metabolism without formation of active metabolites. Elimination in children is faster than adults.[44] The drug does not affect the serum level of phenytoin, carbamazepine or other lipid-soluble drugs such as warfarin but decreases the serum level of valproate by 10%. However, this effect is not clinically significant. The starting dose is 7-15 mg/day in 3 doses titrating upward by 5-15 mg/day each week up to 30-60 mg/day.[45,46] This drug is not recommended for children under 12 years. The adverse effects are mainly CNS related and include: tremor, dizziness, sedation, somnolence, confusion, irritability and depression. Most side effects can be minimized by slower dose titration. There has been no reported severe idiosyncratic reaction with tiagabine. There is no evidence for its teratogenicity in animal models or human studies.[47,48]

Levetiracetam (Keppra, LVT). It is a pyrrolidone derivative with a chemical name alpha-ethyl-2-oxo-1-pyrrolidone acetamide,[49] bioavailability of this drug reaches up to 95% and it does not bind to proteins in the plasma, its half life is 6-8 hours, it is partly hydrolyzed in the blood into inactive metabolites, 66% of the drug secreted in the urine unchanged, and its therapeutic monitoring range is 20-60 mg/liter.[16] Dosage adjustment and extra attention are necessary in patients with decreased renal function.[16]

Levetiracetam is effective as an add-on therapy for partial epilepsy, especially refractory types, in a dose range of 1000-3000mg, this drug does not need titration to the dose but clinical observation will judge the dosing schedule, it is effective in 500mg, 1000mg, or 1500 twice daily,[50-52] and it can be taken with or without food. The main side effects are susceptibility to infection, rhinitis, or flu-like symptoms, sedation, fatigue, incoordination,

psychosis, anemia and leukopenia, and there is no known drug interactions with LVT.[53] Data regarding LVT use in children, elderly and pregnancy is incomplete.[16]

Treatment strategy. Despite the advances in drug development, 20-40% of patients with epilepsy are not adequately treated. The common reasons for inadequate treatment include: incorrect diagnosis, inappropriate drug selection, when long-term AED treatment is not optimal or the patient is not responsive to the AED regimen, or both.

Ideally, the goal of therapy is to develop a therapeutic regimen eliminating all seizures with no side effects, resulting in the best possible quality of life for the patient. Accurate classification of seizure type and consideration of precipitating factors, etiology, age of onset, family history and interictal EEG abnormalities are crucial to the proper diagnosis of seizures and prognosis with therapy. Early, accurate and complete diagnosis and effective treatment is necessary for maximum seizure control. With successful, comprehensive treatment, the optimal quality of life goals can be achieved.

Monotherapy with AEDs should always be attempted first in treatment-naive patients as the advantages include avoidance of drug-drug interactions, fewer adverse drug reactions, easier administration and decreased cost. Older AEDs that are FDA-approved as monotherapy include: carbamazepine, phenobarbital, phenytoin and valproate. These agents have been used extensively for many years. Many patients have been successfully treated with these older agents, however, the percentage of patients that remain seizure-free decreases overtime. Within the last decade several new agents have been developed for the treatment of seizures. Most of these new agents are currently FDA approved as add-on (adjunctive) therapy only. These agents include: GBP, LTG, TPM, FBM, TGB, ZON, OXB and LVT. Oxcarbazepine and FBM also have specific monotherapy indications. Compared to standard AEDs, these newer agents generally offer more favorable pharmacokinetic and side effect profiles, and may prove to be useful as monotherapy for multiple seizure types. However, they are expensive and have not been used as extensively.

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