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REVIEW ARTICLE

ANTIEPILEPTIC DRUG THERAPY IN THE TWENTY FIRST CENTURY

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Abstract : In the last 25 years, particularly the last decade, there have been many advances relating to all aspects of epilepsy ie. pathophysiology, diagnosis, pharmacotherapy and surgical interventions. Noteworthy has been the progress in terms of understanding of the established antiepileptic drugs (AEDs) and introduction of several newer agents developed rationally, on the basis of now available information on the biochemical changes in the epileptic brain. Data is accumulating regarding the use of newer agents but they still need to stand the test of time. Many of the newer AEDs may offer a better tolerability because of favorable pharmacokinetic characteristics and minimal drug interactions. However, serious adverse events have been associated with felbamate and lamotrigine already and for other newer agents reliable and accurate data needs to be generated.

Key words : antiepileptic drugs (AEDs) newer AEDs epilepsy

INTRODUCTION

Epilepsy has been known to the mankind for centuries. Most western studies report the overall incidence of epilepsy to be around 20–50 cases per 100,000 persons, in a general population per year (excluding febrile seizures and single seizures). The usual prevalence figure from these countries is 500 cases per 100,000 persons in the population. In India, studies have reported prevalence rate varying from 171 to 978 cases per 100,000 population. Going by an average figure of 500 cases per 100,000 population, the number of epilepsy patients in the whole of India will be about 5,000,000 (in an estimated population of 1,000,000,000). All these statistics points to the fact

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that epilepsy is one of the commonest neurological disorders, in any country, including India.

This is also perhaps the only disease, plagued with maximum superstitions, anomalies and idiosyncrasies. A wide variety of modalities for arresting and controlling seizures have been employed, for example- naturopathy, yoga, drugs and surgery but drug therapy remains the mainstay in treatment of epilepsies. In recent years, much advancement has taken place in understanding the etiopathogenesis of seizure disorders that have more or less rationalized the development of antiepileptic drugs. These newer developments with their advantages and limitations are discussed.

The conventional antiepileptic drugs (AEDs)

The presently available AEDs ie. phenobarbitone, phenytoin, benzodiazepines, sodium valproate, carbamazepine, ethosuximide and trimethadione, are associated with a number of shortcomings. They are unable to control seizures effectively in as many as 25% of the patients (1), their dose related neurotoxicity and other side effects, at times, become a major limitation in their clinical use (2). Furthermore, since AED therapy is for a long duration, there is a risk of drug interactions, with concomitant administration of other drugs (3). This problem is further compounded by the high protein bindings for some drugs and potential for inducing hepatic enzymes. The comparative features of the most commonly used AEDs are listed in Table I and the major drug interactions in Table II.

These limitations with the conventional AEDs, highlighted the need for developing newer agents for epilepsies and the AED search has come a long way, particularly over the last two decades. The nineties have witnessed a significant addition to the therapeutic armamentarium against epilepsies. But, first what properties/features are desirable in an AED.

An ideal AED

An ideal AED should have favorable profile not only in terms of clinical efficacy but from pharmacokinetic, toxicologic, pharmaceutical and economics point of view as well. The features of an ideal AED are listed in Table III.

TABLE I: Profile of conventional AEDs.

	Phenobarbitone	*Phenytoin*	*Carbamazepine*	*Valproate*
Seizure free	36%	38%	47%	23%
Protein bound	50%	90%	50%	90%
Enzyme inducer	+++	+++	+++	–
Sedation	Severe	Modest	Modest	Modest
Toxicity	Connective tissue	Liver	Marrow	Liver, pancreas,
Teratogenicity	Decreased IQ	Hydantoin syndrome	Neural tube defects	Neural tube defects

TABLE II: Drug interactions with conventional AEDs.

Antiepileptic drugs	*Concomitant drugs*	*Interaction*
Phenobarbitone	Alcohol Antihistamines Opioids	Additive action with phenobarbitone. Marked CNS depression and impaired motor activity.
	Tolbutamide	Increased metabolism of tolbutamide. Vitiate diabetes control.
	Oral contraceptives (OCP)	induces metabolism of OCP. Contraceptive failure may occur.
	Griseofulvin	Decreases absorption of grisefulvin from the GIT therefore, reduced effectiveness.
	Sodium valproate	Increases plasma concentration of Phenobarbitone.
Valproic acid	Phenytoin	Reduced metabolism and increased toxicity of Phenytoin.
	Carbamazepine	Inhibits the metabolism of carbamazepine. The combination may lead to teratogenicity
Primidone	Aspirin	Valproate is displaced from protein binding sites increasing free drug.
		Enhanced conversion to Phenobarbitone.
Diazepam	Phenytoin	Lower Serum valproate levels is reduced.
	Valproate	Synergistic effects. Concurrent use provokes psychotic
	Alcohol	symptoms.
Phenytoin	Insulin	Inhibition of insulin secretion causes hyperglycemia.
	Tolbutamide	Phenytoin inhibits metabolism leads to hypoglycemia.
	OCP	Enhanced metabolism of OCP due to induction of microsomal enzymes. Contraceptive failure.
	Corticosteroids	Can increase phenytoin concentration by 40%.
	Lithium	Precipitation of lithium toxicity.
	Theophylline	Increases the rate of clearance of theophylline.
	Sucralfate	Decreases Phenytoin absorption.
	Antacids	May decrease Phenytoin absorption.
Carbamazepine	Antacids	Reduces plasma concentration of haloperidol due to enzyme
	Haloperidol	induction.
	OCP	Induces metabolism of OCP.
	Phenytoin	Increase the metabolism of carbamazepine & vice versa.
	Valproate	Lowers the concentration of valproate.
	Erythromycin	Carbamazepine metabolism inhibited.

The newer AEDs

Strategies for development of newer AEDS:

The conventional AEDs like phenytoin, carbamazepine, trimethadione, ethosuximide were identified by screening procedures in animal models and valproate through serendipity. But, with increased understanding of pathophysiology underlying epilepsies, these approaches have, to a great extent, been replaced by "mechanism based approaches". The mechanism based approaches rely on, the basic premise that, epilepsies are due to an imbalance between excitatory and inhibitory transmission in the brain (Fig. 1). Key inhibitory and excitatory players in the brain are gamma aminobutyric acid (GABA) and excitatory amino acids (EAAs) respectively (4). Thus, for developing newer AEDs, the basic approach becomes either augmenting GABAergic transmission or inhibition of excitatory amino acid transmission (Fig. 2). This can be achieved

TABLE III : Properties of an ideal AED.

•	Efficacy and selectivity
•	Long t1/2
•	Low protein binding
•	No hepatic enzyme induction
•	Minimal side effects
•	Teratogenicity nil
•	No drug interactions
•	NEUROPROTECTIVE

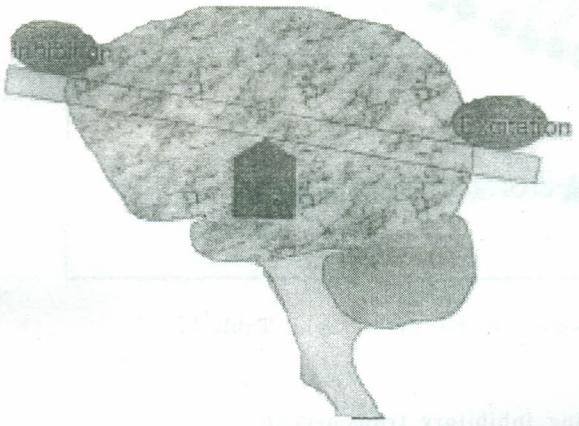

Fig. 1 : Imbalance between the excitation and inhibition is the hallmark of epilepsy.

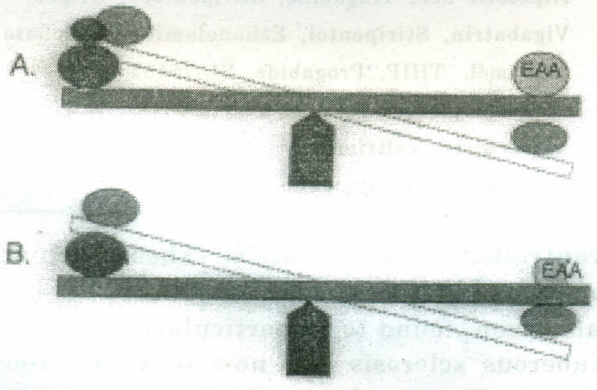

Fig. 2 : The two rational approaches to correct the imbalance forms approach to antiepileptic drug development. A. Enhancing GABAergic transmission, B. Decreasing excitatory amino acids.

by a number of methods (Fig. 2 and 3). The drugs based on these approaches are listed in Table IV and V.

In addition, modulation of some ionic channels eg. Sodium, potassium, and calcium channels has also been found useful for AED development. Drugs modulating ionic channels include, oxcarbazepine, zonisamide, ralitoline, flunarizine and topiramate.

Newer AEDs Developed by mechanistic approach

Eight new AEDs have been licensed in the past ten years, all over the world. These include felbamate, gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin and zonisamide. Many others are in various stages of development eg. remacemide, losigamone, stiripentol, flunarizine, loreclezole, levetiracetam (UCB LO59) etc. (5–7). The pharmacokinetic profile of some of these agents, their indications, major side effects and drug interactions are summarized in Table VI, VII and VIII. The individual agents are discussed.

Vigabatrin (VGB)

Vigabatrin, chemically, 4–amino–5-hexenoic acid is a synthetic derivative of GABA and has a broad spectrum of antiepileptic activity. It acts as a suicide inhibitor of GABA–transaminases and prevents degradation of GABA. The resultant prolonged increase in brain levels of this neurotransmitter reduce the hypersynchronous disch-arges and seizure activity. VGB is a raecmic mixture and only the S (+) enantiomer is

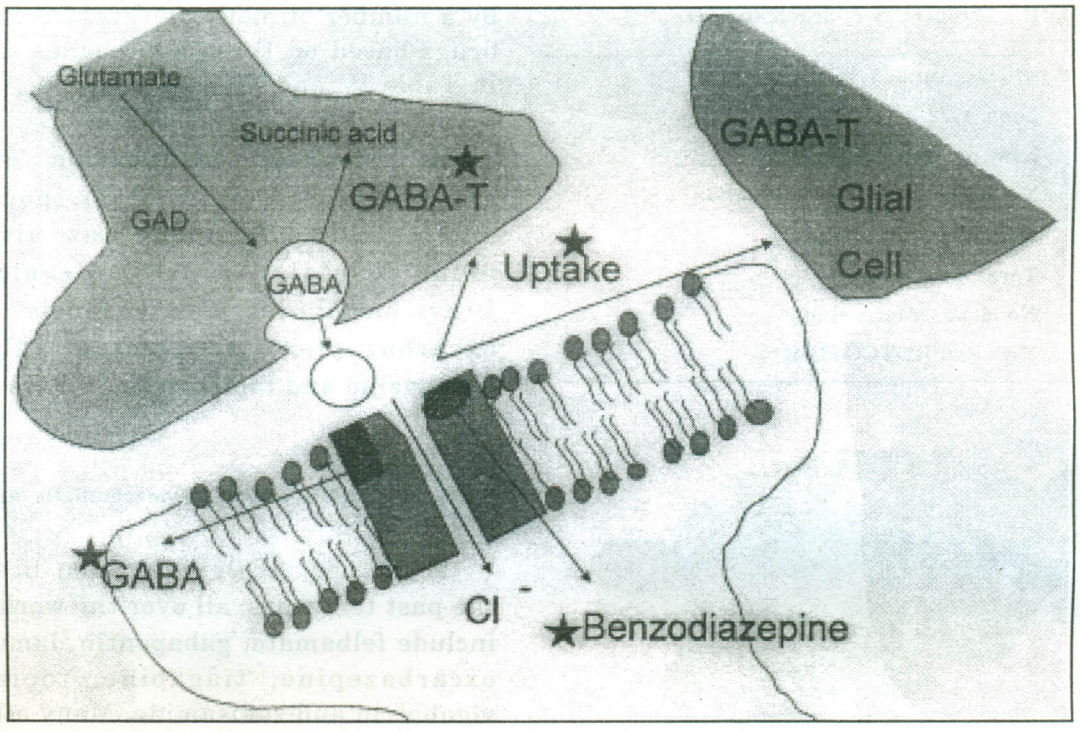

Fig. 3 : Methods for augmenting GABAergic transmission. For details refer Table IV.

TABLE IV: Methods for increasing inhibitory transmission.

Strategies	*Drugs*
Inhibit GABA reuptake	Nipecotic acid Tiagabine, Stiripentol ?, CI-966
Inhibit GABA-transaminases	Vigabatrin, Stiripentol, Ethanolamine-0-sulphate
$GABA_A$ receptor agonist	Muscimol, THIP, Progabide, SL-75102
Benzodiazepine agonist	Clobazam, Flumazenil
Non-GABAergic mechanism	Milacemide, Taltrimide
Others	Gabapentin, Losigamone

pharmacologically active. By virtue of it being a suicide inhibitor, it has a long duration of action. An additional effect is reduction in brain levels of aspartate, glutamate and alanine (8).

VGB is indicated as an add-on therapy in certain forms of epilepsies, not satisfactorily controlled by other AEDs. These include complex partial seizures in children. It has also been found to be particularly useful in tuberous sclerosis and now is a first line drug in West syndrome (9). The advantages with vigabatrin are an early onset of anticonvulsant effect and a low rate of interactions with other AEDs. But,

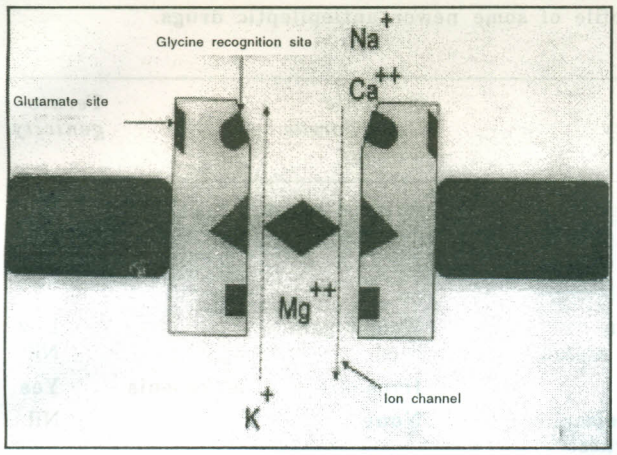

Fig. 4: Different sites for inhibition of excitatory transmission at the NMDA receptor. For drugs acting at these sites refer Table V.

development of tolerance in upto one third of responders is reported (10). The major side effects are somnolence, agitation, insomnia, ataxia, nausea, blurred vision, dizziness, headache and rarely psychosis (11, 12). It is best avoided in patients with a history of psychiatric disorders and caution when used in elderly and those with poor renal function.

In experimental animals ie. mice, rats and dogs, chronic administration at doses of 50–100 mg/kg/day, led to development of intramyelinic edema and stoppage of additional studies on this drug in the U.S. in 1983. However, this side effect has not

TABLE V: Methods for decreasing excitatory transmission in the brain.

Strategies	*Drugs*
Decreased synaptic release	Lamotrigine
Uncompetitive blockade of Ion channel	Dizocilpine (MK801), ADCI, PPA 3-F-PCA, Dextromethorphan
Blockade at glutamate (NMDA) recognition site	Remacemide, AP5, AP7, CGP 37849, CGP 39551, CGP 19755, CPP, D-CPPene, NPC 12626
Blockade at glycine co-agonist site	HA-966, L-687, 414, Felbamate?
Blockade at polyamine modulatory Site	Ifenprodil

TABLE VI: Comparative pharmacokinetic profile of some newer antiepileptic drugs.

Drugs	*Dose (mg/day)*	*Elimination half-life(h)*	*Protein binding(%)*	*Enzyme induction*
Felbamate	2400–4800	11–18	35	Inhibits
Flunarizine	10–15	~50	99	–
Gabapentin	900–2400	4–6	Nil	No effect
Lamotrigine	100–600	15–60	55	Mixed
Losigamone	1500	4–5	60	–
Oxcarbazepine	300–1800	10–15	–	No effect
Ralitoline	600–900	4–6	74	–
Remacemide	600	4–6	–	–
Stiripentol	2000–3000	Variable	>90	–
Tiagabine	24–80	5–14	–	No effect
Topiramate	600–1200	19–23	–	No effect
Vigabatrin	2000–4000	5–7	–	No effect
Zonisamide	400–600	27–36	–	Minimal

TABLE VII: Indications and toxicity profile of some newer antiepileptic drugs.

Drugs	*Indication/ Seizure type*	*CNS toxicity*	*Systemic toxicity/organ damage*	*Terato-genicity*
Felbamate	Partial, tonic clonic	Insomnia, agitation, headeche	Aplastic anemia, hepatic damage	Nil
Flunarizine	Partial, tonic clonic, reflex epilepsy	–	–	–
Gabapentin	Partial, tonic	Mild sedation	Weight gain	Low
Lamotrigine	Partial	Drowsiness, ataxia	Rash	Nil
Oxcarbazepine	Partial, tonic clonic	Minimal	Hyponatremia, leukopenia	Yes
Tiagabine	Partial, tonic	Sedation, tremor, mental slowness	None	Nil
Vigabatrin	Partial	Depression, psychosis (rare), irritability	Weight gain	Yes
Zonisamide	Partial, progressive myoclonic	Drowsiness, memory impairment, cognitive dysfunction	Renal calculi	?

TABLE VIII: Drug interactions with newer AEDs.

Anti epileptic drugs	*Concomitant drugs*	*Interaction*
Lamotrigine	Valproate	Block degradation of lamotrigine. Increases the risk of severe rash induced by lamotrigine.
Tiagabine	Phenobarbitone	t ½ of taigabine decreases because of enzyme induction.
	Carbamazepine	Decreases t ½ of tiagabine.
Oxcarbazepine	Phenobarbitone	High doses of oxcarbazepine increase metabolism of phenobarbitone by inducing CYP2C19.
	Phenytoin	High doses of oxocarbazepine increase metabolism.
Felbamate	Phenytoin	30–50% increases in levels of felbamate due to inhibition of hepatic metabolism.
	Phenobarbitone	30–50% increases in levels of phenobarbitone by inhibiting hepatic metabolism.
	Valproate	30–50% increases in levels of valproate by inhibiting hepatic metabolism.
Vigabatrin	Phenytoin	20% reduction in the levels of Phnytoin. Mechanism unclear.
	Tiagabine	Pharmacodynamic interaction.
	Gabapentin	Pharmacodynamic interaction.
Zonisamide	Carbamazepine	Levels of Zonisamide decrease due to enzyme induction by carbamazepine.
	Phenobartitone	Levels of Zonsamide decrease due to enzymes induction.
	Phenytoin	Zonisamide causes slight increase in levels of phenytoin.

been encountered in humans (13–16). Due to reports of teratogenicity in some animal models, it is not recommended for women of child bearing age (17).

Gabapentin (GBP)

GBP, designed to facilitate GABA–mediated inhibition, is structurally similar to GABA (18). It has high lipid solubility so that it can cross blood brain barrier freely, unlike GABA. The exact mechanism of action of GBP remains unknown. Biochemical studies, negate the initial hypothesis of a direct GABA mimetic activity (19). An alternative could be, an increase in GABA synthesis, by a hitherto unknown mechanism. Novel and specific binding sites for GBP on neuronal membranes in brain areas with excitatory synapses, have been characterised (20, 21). Some experiments suggest an involvement of the strychnine insensitive glycine site of the NMDA receptor in the anticonvulsant activity of this drug (22).

GBP may be useful as add–on therapy in patients with drug resistant partial epilepsy, with or without generalization. A considerable benefit with GBP monotherapy in partial seizures is also documented (23). The side effects encountered are mainly CNS ie. drowsiness, ataxia, fatigue, dizziness and weight gain (24). Some gastro-intestinal (GI) symptoms may also occur. The side effects are transient and do not require discontinuation of the drug. Due to lack of information on its teratogenic potential, use in pregnant women is contraindicated. Patients with renal impairment require dose adjustment. GBP is free of interactions with other drugs and its addition to an existing AED regimen does not require dose adjustment (25).

Apart from the anticonvulsant effect, GBP is also used in acute intermittent porphyria, reflex sympathetic dystrophy and other neurogenic pain syndromes (26–28).

Lamotrigine (LTG)

LTG, a phenyltriazine, is a novel AED structurally unrelated to the available AEDs. It was initially synthesized as a folic acid antagonist but, its anticonvulsant activity is independent of antifolate activity (19). LTG acts directly on voltage-activated sodium channels, inactivates them, thus inhibiting sustained, repetitive action potential firing (29–31). The presynaptic release of excitatory neurotransmitters, namely glutamate, is reduced, that may be followed by reduction in nitric oxide synthesis (32). The effect of LTG on sodium channels is not mediated by NMDA receptors.

A sizeable body of evidences have demonstrated a considerable similarity between mechanism of action of LTG, phenytoin and carbamazepine. The broader spectrum of anticonvulsant activity of LTG and a reduced side effect burden as compared to these drugs however suggests some additional, as yet unidentified mechanisms for anticonvulsant action. Furthermore, LTG is cerebroprotective in several rodent models of ischaemia (29, 33, 34).

LTG is active against both partial seizures and secondarily generalized seizures. Though, it is indicated only as add-on therapy in partial seizures, but, it may be effective

monotherapy in partial tonic-clonic and absence seizures and drug resistant seizures in epilepsy syndromes with multiple seizure types (35). In the pediatric population, LTG is most effective against absence seizures, Lennox–Gastaut syndrome and other symptomatic secondarily generalized epilepsies. It is also effective against infantile spasms and in rett syndrome (23).

The side effects with LTG are fairly mild, dose related and include diplopia, drowsiness, dizziness, ataxia, headache, nausea and vomiting (24). Approximately 5 % of patients develop a rash that subsides on discontinuation of treatment and rarely, bullous erythema multiforme, Steven's Johnson syndrome or angioedema develop (36). Since LTG does not alter the pharmacokinetics of other AEDs, it has good potential as adjunct therapy. But, valproate blocks degradation of this drug and thereby increases its half–life. This may be useful in combination therapy but, it is to be remembered that valproate also increases the risk for severe rash with LTG (37).

Felbamate (FBM)

FBM is a dicarbamate, exhibiting structural similarity to meprobamate but is distinct pharmacologically. It has a unique and wider spectrum of activity and uncommonly low sedative effect. Indirect evidences point towards effect on voltage–dependent sodium channels as a possible mechanism. However, recently modulation of function of NMDA receptor, by antagonism at a glycine site on this receptor has been suggested as a more plausible mechanism (38). A potentiation of chloride currents mediated by GABA has also been observed with FBM (39, 40).

In keeping with its preclinical profile, FBM is effective in refractory patients. In Lennox-Gastaut syndrome also (which is particularly drug resistant), FBM is effective. Other indications include atonic seizures, atypical absence seizures and generalizd tonic–clonic seizures. The most frequent side effects with FBM are nausea and vomiting, insomnia, dizziness, anorexia, weight loss, somnolence, fatigue, lethargy, nervousness, ataxia and diarrhoea (24). More serious are aplastic anemia and hepatic failure, which warrant caution in use (41).

In addition to an anticonvulsant effect, in animal models, FBM has also demonstrated a prominent neuroprotective effect (42, 43). As far as potential for drug interactions is concerned, doses of most anticonvulsants need to be reduced by 30 % when FBM is added.

Oxcarbazepine (OCB)

OCB is a keto analogue of carbamazepine and effectively a prodrug. It is 100 % absorbed and rapidly metabolized to active monohydrate derivative (MHD), which is the true antiepileptic compound (44). The action appears to be similar to carbamazepine ie. acts both presynaptically and postsynaptically by blocking sodium channels. Adenosinergic system may also contribute to its anticonvulsant action (45).

The clinical efficacy and spectrum of this drug is similar to that of carbamazepine, thus it is useful in patients with partial and generalized seizures. It is also effective in patients of trigeminal neuralgia with pain,

acute mania and affective disorders. The major advantage of this drug over carbamazepine is lesser propensity for causing allergic reactions and relatively les drug interactions (46, 47). Thus it is useful in patients who are unable to tolerate carbamazepine. The side effects with OCB are drowsiness, dizziness, ataxia, hyponatremia and mild and transient skin reactions. Modest leukopenia is also observed (48). There are indications of teratogenicity in animal models particularly at high doses (17).

Zonisamide (ZSM)

ZSM is a benzisoxazole, with an antiepileptic profile most similar to phenytoin or carbamazepine (49, 50). It appears to block the propagation/spread of seizure discharges and to suppress the epileptogenic focus. The exact mode of action remains unclear. However, involvement of T–type calcium currents may be a possibility (51). ZSM is neuroprotective in a rat model of ischemia (52).

In clinical trials, ZSM is effective in generalized or compound combination seizures. It is also useful in West syndrome, Lennox-Gastaut syndrome and progressive myoclonus epilepsy (53). The side effects associated with ZSM are drowsiness, memory impairment, worsening of seizures, ataxia, increased salivation, Steven's Johnson syndrome and renal calculi (46). The latter led to cessation of early trials in the U.S. But, later studies have not substantiated the occurrence of kidney stones (23). ZSM is also reported to adversely affect cognitive function, acquisition and consolidation though tolerance to this effect may develop. Drug monitoring is must with the use of this drug. Caution is advised in patients with hepatic dysfunction and in pregnancy (54). ZSM may be effective in mania (55).

Clobazam (CBZ)

CBZ is a benzodiazepine, fundamentally similar to diazepam, nitrazepam or clonazepam (56). It is however less sedating. Reasonable efficacy is reported in patients with atypical absence seizures, atonic, myoclonic and tonic seizures, which are often most difficult to treat (57). CBZ is also effective in children with catastrophic type of epilepsy. The side effects with this drug are similar to other benzodiazepines and tolrance does develop making its long term value questionable (58, 59). However, efforts are on to design dosing schedules and alternative ligands for benzodiazepine receptors, which obviate development of tolerance (60).

Tiagabine (TGB)

TGB is nipecotic acid linked to a lipophilic anchor, to facilitate penetration into the brain on systemic administration. Nipecotic acid inhibits GABA reuptake, particularly into glial cells by inhibition of GABA transporter GAT–1, thereby enhancing the effect of this transmitter (61). TGB is a potent anticonvulsant in most animal models (62–64). Initial therapeutic results in patients are encouraging, with significant reduction in seizure frequency of complex partial seizures and that of secondarily generalized seizures. Toxicity is mild, mainly neurotoxicity ie. sedation, tremor, mental slowness, tiredness, nervousness and headache (65). The drug has demonstrated

no tertogenic/mutagenic potential in animal studies (17). The kinetics is linear and half-life rather short, necessitating frequent dosing. No major interactions reported except increased drug requirement when co-administered with enzyme inducers (66, 67).

Remacemide (RCM)

RCM is an acetamide compound. It weakly blocks NMDA receptors in a non competitive manner and inhibits rapid firing of sodium channels (68). RCM is metabolically transformed to a desglycine compound, FPL 2495A, which is a more potent NMDA receptor antagonist (68). The desglycinated derivative is more potent than the parent compound but also has more CNS toxicity. Studies suggest that RCM is an inducer of hepatic metabolism. Clinical studies with this drug are underway.

Losigamone (LSG)

LSG is unusual in that it is related to naturally occurring compounds (69). Some evidences suggest that the activity of LSG may be mediated by GABA–gated chloride channels. High doses in animals were associated with ataxia, lethargy and emesis. Little organ toxicity is noted and no mutagenic activity. Human volunteers have tolerated LSG in doses upto 1000 mg. Mild dizziness, tiredness and some GI disturbances are observed. Other side effects are headache and diplopia (70). Clinical efficacy needs to be further established.

Ralitoline (RLT)

RLT is a structurally novel compound, derived from compounds known to modify ion transport mechanisms (71). It is 3 to 6 times more potent than phenytoin and carbamazepine in MES test and also effective in chemically induced seizures, except those by pentylenetetrazole. Preliminary studies in patients are underway and appear promising.

Topiramate (TPM)

TPM is a sulfamate-substituted monosaccharide. Four potential mechanisms of actions have been suggested for TPM. These are interaction with GABA receptors, blockade of voltage-activated sodium channels, weakly inhibits carbonic anhydrase and also block kainate/ AMPA receptors (46). In experimental seizures, it has a profile similar to phenytoin. Clinically, it is effective in generalized as well as partial seizures (72, 73). Major side effects are CNS toxicity i.e. dizziness, drowsiness, headache (24). Weight loss and psychic disturbances have also been reported. Rarely, urolithiasis occurs. Though TPM is probably the most effective new AED in the treatment of chronic focal epilepsies and has minimal interaction with other AEDs but the adverse effects may limit its use (74).

Flunarizine (FNZ)

FNZ, a difluorinated piperazine has been used for vertigo and migraine. But, in some add on trials, this drug was found to be effective in patients with partial seizures (75, 76) and also in refractory infant epilepsies (77). The anticonvulsant effect may be due to the calcium channel blocking activity.

Stiripentol (STP)

STP is also structurally unrelated to other AEDs. It is active in many models of

absence epilepsy (78) and, its principal utility appears to be against absence both typical and atypical (79, 80). The major side effects with stiripentol are sedation and GI problems while anorexia, nausea and lethargy have also been reported.

Loreclezole (LCL)

LCL is a triazole derivative believed to modulate GABA receptor activity (81). In preliminary studies, LCL has shown modest efficacy and may be useful as monotherapy.

Levetiracetam (UCB LO59)

UCB L059 belongs to the racetam family and its locus of action may be a non–L–type voltage dependent calcium channel or potassium efflux. In rodent models, anticonvulsant effect is observed (82, 83).

TABLE IX: AEDs abandoned during development stages.

Drug	*Reason for abandoning*
Flunarizine	Mild efficacy
Milacemide	Marginal efficacy
MK 801	Psychosis
Nafimidone	Narrow therapeutic range
ORG 6370	Anticholinergic side effects
Progabide	Poor efficacy, hepatotoxic
Ralitoline	Short half-life

Thus, it is apparent that most newer antiepileptic agents are primarily as add-on therapy with the existing drugs. Monotherapy trials with these agents and trials in specific subset of patients namely pediatric and the elderly are either ongoing or planned. In terms of toxicity profile, though the spectrum of adverse events with these agents is different, their chronic side effect profile is still to be established and so is their actual place in therapy.

Of the newer agents, development of some compounds has practically been abandoned due to limiting side effects or sub-optimum efficacy in clinical trials. Table IX lists such compounds and reasons for abandoning their development.

AED development – The next Millennium

Basic research in epilepsy is also proceeding at a rapid pace and many new targets for AED development have been identified. One of the most significant advancement is the concept of an endogenous anticonvulsant substance and potential of adenosinergic system in this regard (2, 84-86). Furthermore, with the advent of neurobiological techniques, there has been a tremendous increase in our knowledge on possible molecular defects in epilepsies and a substantial number of molecular targets for AED development and screening have been identified. These include ion channels, neurotransmitter receptors, neurotransmitter transporters, ion exchangers and a range of enzymes involved in transmitter metabolism or in protein phosphorylation (87, 88). Some major molecular targets for AED development are listed in Table X.

Here, it would be worthwhile to mention that within these molecular components, there is a diversity of targets. This is so because of the hetrogenity within each group. For example 40 mammalian K^+ cahannels have been identified. The subunit

TABLE X: Molecular targets for AED development.

Ion channels
Voltage dependent Na^+, K^+ and Ca^{2+} channels
Neurotransmitter receptors
GABA receptor
EAA receptors-NMDA, AMPA, Metabotropic
Steroid receptors
Neutrotrophins Trk receptors
Neurotransmitter transporters
GABA transporter
Glutamate transporter
Serotonin transporter
Ion exchangers
Na^+/H^+ exchangers
Na^+/Ca^{2+} exchanger
Enzymes related to neurotransmitters/neuromodulators
GABA transaminase
Glutaminase
Carbonic anhydrase
Adenosine deaminase
Other enzymes
CAM kinases, PKC, PKA, Phosphatases, Adenylate cyclase
Cytokines
Transcription factors

structure of these components is another source of diversity. Studies have revealed that AEDs are target specific subunits. This selectivity of action, related to subunit composition may also influence the spectrum of anticonvulsant activity and the side-effect profile.

Genetic defects as targets for AED development

Though genetecists have identified some candidate genetic defects in pathogenesis of epilepsy, AED development, targeting these does not appear to be lucrative. The primary reason for this is that the genetic defect may be a relatively remote cause of the epileptic phenomenon, exerting its effect at an early developmental stage or through some relatively non specific pathology. Nevertheless, efforts in this direction are ongoing.

Conclusions

Though each new drug introduced has its unique advantage, the disadvantages are still there. Thus none has proved to be the ultimate drug for epilepsies and search for better, novel AEDs is ongoing. As for the trend in AED development, focus has shifted towards identifying possible defects. This will lead to development of AEDs or treatments that block or reverse the process of chronic epileptogenesis. The endeavour of the scientists to have antiepileptic drugs with 100% efficacy, safety, tolerability, and affordability for the epileptic patient in the twenty first century.

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