Review article

Newer antiepileptic drugs

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Abstract

Epilepsy is a very common neurological disorder with high prevalence and incidence. Several conventional antiepileptic drugs are being used for the treatment of various types of epilepsies. Over the last two decades, there has been a rapid expansion in the number and types of available antiepileptic drugs (AED). Newer AEDs are now available for the treatment of various forms of epilepsies. Lamotrigine and topiramate are effective as initial monotherapy for generalized seizures and topiramate, lamotrigine, oxcarbazepine and gabapentin for partial onset seizures. These newer drugs are quite effective and safer than conventional antiepileptic drugs. Many other newer AEDs are under investigation.

Key words:
Epilepsy, Lamotrigine, Newer Antiepileptic Drugs

Introduction

Epilepsy is one of the most common neurological disorders with reported prevalence of 6-8/100,000 incidence of 30-50/100,000 per year and cumulative incidence of 3%. It requires prolonged and sometimes life-long drug therapy. The term seizure refers to a transient alteration of behaviour due to the disordered, synchronous, and rhythmic firing of populations of brain neurons. The term epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures.

More than 40 distinct forms of epilepsy have been identified. Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment. Compliance with medication is a major problem because of the need for long-term therapy together with unwanted effects of many drugs.

Several conventional antiepileptic drugs are being used for the treatment of various types of epilepsies. Effective pharmacological treatments for epilepsy were identified with the bromides in the mid-1850s and phenobarbital in 1912. Over the last two decades, there has been a rapid expansion in the number and types of available antiepileptic drugs (AEDs).

Twenty-five to 40 percent of patients with epilepsy continue to have seizures despite optimal treatment with traditional antiepileptic drugs. Treatment with standard anticonvulsants such as phenytoin, carbamazepine, valproic acid and phenobarbital is often complicated by side effects (narrow safety margin) and by failure to adequately control seizures. Up to 61 percent of patients with seizures report having side effects with antiepileptic drugs. New antiepileptic drugs are now available for the treatment of various forms of seizures and the epilepsy syndromes. Lamotrigine and Topiramate are effective as initial monotherapy for generalized seizures, and Topiramate, Lamotrigine, Oxcarbazepine and Gabapentin for partial onset seizures. Zonisamide is effective as an add-on therapy for patients with partial seizures and may additionally acts as a free radical scavenger thereby provide additional protection of neurons.

Table 1:

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Earliest approved use of drug (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>1993</td>
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<tr>
<td>Lamotrigine</td>
<td>1994</td>
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<tr>
<td>Gabapentin</td>
<td>1994</td>
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<tr>
<td>Fosphenytoin</td>
<td>1996</td>
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<tr>
<td>Topiramate</td>
<td>1996</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>1997</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1999</td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td>2000</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>2000</td>
</tr>
<tr>
<td>Stiripentol</td>
<td>2001 (UK)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>2004</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>2008</td>
</tr>
<tr>
<td>Eslicarbazepine acetate</td>
<td>2009</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>2009</td>
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</tbody>
</table>

LAMOTRIGINE

Pharmacological Effects and Mechanisms of Action: Lamotrigine blocks sustained repetitive firing of mouse spinal cord neurons and delays the recovery from inactivation of recombinant Na+ channels, mechanisms similar to those of phenytoin and carbamazepine. This may well explain lamotrigine’s actions on partial and secondarily generalized seizures. One possibility involves lamotrigine’s inhibition of glutamate release in rat cortical slices treated with veratridine, a Na+ channel activator; raising the possibility that lamotrigine inhibits synaptic release of glutamate by acting at Na+ channels themselves.
Table 2:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Molecular target and activity</th>
<th>Newer antiepileptic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Na(^+) channel modulators that enhance fast inactivation</td>
<td>Lamotrigine, felbamate, oxcarbazepine, topiramate</td>
</tr>
<tr>
<td>2.</td>
<td>Na(^+) channel modulators that enhance slow inactivation</td>
<td>Lacosamide</td>
</tr>
<tr>
<td>3.</td>
<td>Ca(^{2+}) channel blockers</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>4.</td>
<td>(\alpha_2\delta) ligands</td>
<td>Gabapentin, pregabalin</td>
</tr>
<tr>
<td>5.</td>
<td>GABAA receptor allosteric modulators</td>
<td>Felbamate, topiramate, oxcarbazepine</td>
</tr>
<tr>
<td>6.</td>
<td>GABA uptake inhibitors/ GABA-transaminase inhibitors</td>
<td>Tiagabine, vigabatrin</td>
</tr>
<tr>
<td>7.</td>
<td>NMDA receptor antagonists</td>
<td>Felbamate</td>
</tr>
<tr>
<td>8.</td>
<td>AMPA/kainate receptor antagonists</td>
<td>Topiramate</td>
</tr>
<tr>
<td>9.</td>
<td>Enhancers of HCN channel activity</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>10.</td>
<td>SV2A protein ligand</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>11.</td>
<td>Inhibitors of brain carbonic anhydrase</td>
<td>Topiramate, zonisamide</td>
</tr>
</tbody>
</table>

**Pharmacokinetics:** Lamotrigine is completely absorbed from the gastrointestinal tract and is metabolized primarily by glucuronidation. The plasma t\(_{1/2}\) of a single dose is 24-30 hours. Administration of phenytoin, carbamazepine, or phenobarbital reduces the t\(_{1/2}\) and plasma concentrations of lamotrigine. Conversely, addition of valproate markedly increases plasma concentrations of lamotrigine, likely by inhibiting glucuronidation.

**Therapeutic Use:** Lamotrigine is useful for monotherapy and add-on therapy of partial and secondarily generalized tonic-clonic seizures in adults and Lennox-Gastaut syndrome in both children and adults. Lamotrigine monotherapy in newly diagnosed partial or generalized tonic-clonic seizures is equivalent to carbamazepine or phenytoin, monotherapy.\(^8,9\)

**Toxicity:** The most common adverse effects are dizziness, ataxia, blurred or double vision, nausea, vomiting, and rash when lamotrigine was added to another anti-seizure drug.

**FELBAMATE**
Felbamate is a dicarbamate that was approved by the FDA for partial seizures in 1993. An association between felbamate and aplastic anaemia in at least 10 cases resulted in a recommendation by the FDA and the manufacturer for the immediate withdrawal of most patients from treatment with this drug. Post marketing experience revealed an association between felbamate exposure and liver failure.

**Pharmacological Effects and Mechanisms of Action:** Felbamate is effective in both the maximal electroshock and pentylenetetrazol seizure models. Clinically relevant concentrations of felbamate inhibit NMDA-evoked responses and potentiate GABA-evoked responses in whole-cell, voltage-clamp recordings of cultured rat hippocampus neurons.\(^10\)

**Therapeutic Use:** An active control, randomized, double-blind protocol demonstrated the efficacy of felbamate in patients with poorly controlled partial and secondarily generalized seizures.\(^11\) Felbamate also reduced seizures in patients with Lennox-Gastaut syndrome.

**FLUROFELBAMATE**
Substitution of a fluorine atom for a hydrogen at the 2-position of the propanediol moiety of felbamate to form fluorofelbamate prevents the formation of this reactive aldehyde. Preliminary evidence indicates that fluoroelbamate does not enhance GABA receptor responses. However, like felbamate, fluoroelbamate may inhibit NMDA receptors and might also affect sodium channels.

**CARBAMAZEPINE DERIVATIVE**

a. **OXCARBAZEPINE:** Oxcarbazepine is a prodrug that is rapidly reduced to the 10-mono hydroxy (MHD) metabolite which is responsible for its anticonvulsant activity. MHD blocks sodium channels preventing the spread of the abnormal discharge. Modulation of calcium channels is also a hypothesis. It is approved for use in adults and children with partial onset seizures. Oxcarbazepine is a less potent inducer of CYP3A4 and UGT than carbamazepine. The adverse effects profile is similar to that of other antiepileptic drugs with respect to nausea, vomiting, headache, and visual disturbance.

b. **(S)-LICARBAZEPINE ACETATE** (BIA 2-093): (S)-licarbazepine acetate (BIA 2-093) is also in Phase III clinical
trials. BIA 2-093 only forms (S)-licarbazepine, which is then converted to the trans-diol.\(^\text{12}\) \(^\text{13}\) BIA 2-093 causes a voltage-dependent block of voltage-dependent sodium currents with similar potency to carbamazepine.\(^\text{14}\) In addition, BIA 2-093, as is the case for other sodium channel blocking AEDs, inhibits sodium channel-dependent release of neurotransmitters with similar potency to carbamazepine and oxcarbazepine.\(^\text{15}\)

TOPIRAMATE
Topiramate is a sulfamate-substituted monosaccharide that is FDA-approved as initial monotherapy (in patients at least 10 years old) and as adjunctive therapy (for patients as young as 2 years of age) for partial-onset or primary generalized tonic-clonic seizures, for Lennox-Gastaut syndrome in patients 2 years of age and older, and for migraine headache prophylaxis in adults.

Pharmacological Effects and Mechanisms of Action: Topiramate reduces voltage-gated Na\(^+\) currents in cerebellar granule cells and may act on the inactivated state of the channel similar to phenytoin. In addition, topiramate activates a hyperpolarizing K\(^+\) current, enhances postsynaptic GABA\(_A\)-receptor currents, and limits activation of the AMPA-kainate-subtype(s) of glutamate receptor. Topiramate is a weak carbonic anhydrase inhibitor.

Pharmacokinetics: Topiramate is rapidly absorbed after oral administration, exhibits little (10-20%) binding to plasma proteins, and is mainly excreted unchanged in the urine. The remainder undergoes metabolism by hydroxylation, hydrolysis, and glucuronidation with no single metabolite accounting for > 5% of an oral dose. Its \(t_{1/2}\) is \(~1\) day. Reduced estradiol plasma concentrations occur with concurrent topiramate, suggesting the need for higher doses of oral contraceptives when coadministered with topiramate.

Therapeutic Use: A double-blind study revealed topiramate to be equivalent to valproate and carbamazepine in children and adults with newly diagnosed partial and primary generalized epilepsy.\(^\text{16}\) Additional studies disclosed topiramate to be effective as monotherapy for refractory partial epilepsy and refractory generalized tonic-clonic seizures.\(^\text{17}\) Topiramate also was found to be significantly more effective than placebo against both drop attacks and tonic-clonic seizures in patients with Lennox-Gastaut syndrome.\(^\text{18}\)

Toxicity: Topiramate is well tolerated. The most common adverse effects are somnolence, fatigue, weight loss, and nervousness. It can precipitate renal calculi, which is most likely due to inhibition of carbonic anhydrase. Topiramate has been associated with cognitive impairment and patients may complain about a change in the taste of carbonated beverages.

LACOSAMIDE
Pharmacological Effects and Mechanism of Action: Lacosamide enhances slow inactivation of voltage-gated Na\(^+\) channels and limits sustained repetitive firing, the neuronal firing pattern characteristic of partial seizures. Lacosamide also binds collapsin response mediator protein 2 (crmp-2), a phosphoprotein involved in neuronal differentiation and axon outgrowth.

Therapeutic Use: Double-blind, placebo-controlled studies of adults with refractory partial seizures demonstrated that addition of lacosamide to other drugs was superior to placebo.

GABAPENTIN AND PREGABALIN
Gabapentin and pregabalin are anti-seizure drugs that consist of a GABA molecule covalently bound to a lipophilic cyclohexane ring or isobutane, respectively. Gabapentin was designed to be a centrally active GABA agonist, with its high lipid solubility aimed at facilitating its transfer across the blood-brain barrier.

Pharmacological Effects and Mechanisms of Action: Despite their design as GABA agonists, neither gabapentin nor pregabalin mimics GABA when iontophoretically applied to neurons in primary culture. Analgesic efficacy of pregabalin is eliminated in these mice; whether the anticonvulsant effects of pregabalin are also eliminated was not reported. It is unclear whether the anticonvulsant and analgesic effects of gabapentin and pregabalin are mediated by affecting Ca\(^{2+}\) currents and, if so, how.

Pharmacokinetics: Gabapentin and pregabalin are absorbed after oral administration and are not metabolized in humans. These compounds are not bound to plasma proteins and are excreted unchanged, mainly in the urine. Their half-lives, when used as monotherapy, approximate 6 hours. These compounds have no known interactions with other anti-seizure drugs.

Therapeutic Uses: Gabapentin and pregabalin are effective for partial seizures, with and without secondary generalization, when used in addition to other anti-seizure drugs. Double-blind placebo-controlled trials of adults with refractory partial
seizures demonstrated that addition of gabapentin or pregabalin to other anti-seizure drugs is superior to placebo.\textsuperscript{19,20} A double-blind study of gabapentin (900 or 1800 mg/day) monotherapy disclosed that gabapentin was equivalent to carbamazepine (600 mg/day) for newly diagnosed partial or generalized epilepsy. Gabapentin also is being used for the treatment of migraine, chronic pain, and bipolar disorder.

**Toxicity:** Overall, gabapentin is well tolerated with the most common adverse effects of somnolence, dizziness, ataxia, and fatigue. Gabapentin and pregabalin are listed in pregnancy category C.

**TIAGABINE**

**Pharmacological Effects and Mechanism of Action:** Tiagabine inhibits the GABA transporter, GAT-1, and thereby reduces GABA uptake into neurons and glia. In CA1 neurons of the hippocampus, tiagabine increases the duration of inhibitory synaptic currents, findings consistent with prolonging the effect of GABA at inhibitory synapses through reducing its reuptake by GAT-1. Paradoxically, tiagabine has been associated with the occurrence of seizures in patients without epilepsy and off-label use of the drug is discouraged.

**Pharmacokinetics:** Tiagabine is rapidly absorbed after oral administration, extensively bound to serum or plasma proteins, and metabolized mainly in the liver, predominantly by CYP3A. Its $t_{1/2}$ of $\sim$8 hours is shortened by 2-3 hours when co-administered with hepatic enzyme–inducing drugs such as phenobarbital, phenytoin, or carbamazepine.

**Therapeutic Use:** Double-blind, placebo-controlled trials have established tiagabine efficacy as add-on therapy of refractory partial seizures with or without secondary generalization.

**Toxicity:** The principal adverse effects include dizziness, somnolence, and tremor; they appear to be mild to moderate in severity and appear shortly after initiation of therapy. Tiagabine and other drugs that enhance effects of synaptically released GABA can facilitate spike-and-wave discharges in animal models of absence seizures. Case reports suggest that tiagabine treatment of patients with a history of spike-and-wave discharges causes exacerbations of their EEG abnormalities. Thus, tiagabine may be contraindicated in patients with generalized absence epilepsy.

**VIGABATRIN**

Vigabatrin was approved by the FDA in 2009 as adjunctive therapy of refractory partial complex seizures in adults. In addition, vigabatrin is designated as an orphan drug for treatment of infantile spasms. Due to progressive and permanent bilateral vision loss, vigabatrin must be reserved for patients who have failed several alternative therapies.

**Pharmacological Effects and Mechanism of Action:** Vigabatrin is a structural analog of GABA that irreversibly inhibits the major degradative enzyme for GABA, GABA-transaminase, thereby leading to increased concentrations of GABA in the brain. Its mechanism of action is thought to involve enhancement of GABA-mediated inhibition.

**Therapeutic Use:** The subset of children in whom infantile spasms were caused by tuberous sclerosis was particularly responsive to vigabatrin.

**LEVETIRACETAM**

**Pharmacological Effects and Mechanism of Action:** Levetiracetam exhibits a novel pharmacological profile insofar as it inhibits partial secondarily generalized tonic-clonic seizures in the kindling model, yet is ineffective against maximum electroshock- and pentylentetrazol-induced seizures, findings consistent with clinical effectiveness against partial and secondarily generalized tonic-clonic seizures. The correlation between binding affinity of levetiracetam analogs and their potency toward audiogenic seizures suggests that a synaptic vesicle protein, SV2A, mediates the anticonvulsant effects of levetiracetam.\textsuperscript{21}

**Pharmacokinetics:** It neither induces nor is a high-affinity substrate for CYP isoforms or glucuronidation enzymes and thus is devoid of known interactions with other anti-seizure drugs, oral contraceptives, or anticoagulants.

**Therapeutic Use:** Double-blind, placebo-controlled trials of adults with either refractory partial seizures or uncontrolled generalized tonic-clonic seizures associated with idiopathic generalized epilepsy revealed that addition of levetiracetam to other anti-seizure medications was superior to placebo. Levetiracetam also has efficacy as adjunctive therapy for refractory generalized myoclonic seizures.\textsuperscript{21} Insufficient evidence is available about its use as monotherapy for partial or generalized epilepsy.

**ZONISAMIDE**

Zonisamide is a sulfonamide derivative that is FDA approved as adjunctive therapy of partial seizures in adults.
Pharmacological Effects and Mechanism of Action: Zonisamide inhibits the T-type Ca2+ currents. In addition, zonisamide inhibits the sustained, repetitive firing of spinal cord neurons, presumably by prolonging the inactivated state of voltage-gated Na+ channels in a manner similar to actions of phenytoin and carbamazepine.

Pharmacokinetics: It has a long t1/2 (~63 hours), and is ~40% bound to plasma protein. Approximately 85% of an oral dose is excreted in the urine, principally as unmetabolized zonisamide and a glucuronide of sulfamoylacetyl phenol, which is a product of metabolism by CYP3A4. Phenobarbital, phenytoin, and carbamazepine decrease the plasma concentration/dose ratio of zonisamide, whereas lamotrigine increases this ratio.

Therapeutic Use: Double-blind, placebo-controlled studies of patients with refractory partial seizures demonstrated that addition of zonisamide to other drugs was superior to placebo. There is insufficient evidence for its efficacy as monotherapy for newly diagnosed or refractory epilepsy.

Toxicity: Overall, zonisamide is well tolerated. Approximately 1% of individuals develop renal calculi during treatment with zonisamide, which may relate to its ability to inhibit carbonic anhydrase. Post-marketing experience indicates that zonisamide can cause metabolic acidosis in some patients. Patients with predisposing conditions (e.g., renal disease, severe respiratory disorders, diarrhoea, surgery, ketogenic diet) may be at greater risk.

RUFINAMIDE
Pharmacological Effects and Mechanism of Action: Rufinamide enhances slow inactivation of voltage-gated Na+ channels and limits sustained repetitive firing, the firing pattern characteristic of partial seizures. Whether this is the mechanism by which rufinamide suppresses seizures is presently unclear.

Therapeutic Use: A double-blind, placebo-controlled study of children with Lennox-Gastaut syndrome demonstrated that rufinamide reduced tonic-atonic seizure frequency to a greater extent than placebo.

FOSPHENYTOIN
Fosphenytoin is a prodrug and is rapidly converted to phenytoin in the blood, providing high levels of phenytoin within minutes. Fosphenytoin may also be administered intramuscularly (IM). Phenytoin sodium should never be given IM because it can cause tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration. Due to sound-alike and look-alike names, there is a risk for medication error to occur.

Figure -1 mechanism of action of antiepileptic drugs

STIRIPENTOL
Stiripentol has some efficacy as an adjunctive therapy in children. It enhances GABA release and prolongs GABA-mediated synaptic events in a manner similar to phenobarbital.

It is unrelated to other anticonvulsants and belongs to the group of aromaticallyclic alcohols. In December 2001 the European Medicines Agency (EMA) granted stiripentol orphan drug status for the treatment of severe myoclonic epilepsy in infancy (SMEI, also known as Dravet's syndrome). Side effects are largely due to the increase in plasma concentrations of other anticonvulsants and can be reduced by lowering the dose of those drugs.

RETIGABINE Retigabine (INN) or ezogabine (USAN), codenamed D-23129, is an anticonvulsant used as a treatment for partial epilepsies. Retigabine works primarily as a potassium channel opener—that is, by activating a certain family of voltage-gated potassium channels in the brain.23
### Table 3:

<table>
<thead>
<tr>
<th>Newer Antiepileptic Drugs</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>900-1800 Mg</td>
<td>Begun with a low dose (300 mg once on the first day), which is increased in daily increments of 300 mg until an effective dose is reached.</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Initial dose: 75 mg 2 times a day or 50 mg 3 times a day</td>
<td>Doses of 150 mg to 600 mg/day. The total daily dose should be divided and given either 2 or 3 times a day. Maximum dose: 600 mg/day.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Initially At 50 Mg/Day For 2 Weeks.</td>
<td>Dose is increased to 50 mg twice per day for 2 weeks and then increased in increments of 100 mg/day each week up to a maintenance dose of 300-500 mg/day divided into two doses.</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>500 Mg Bid</td>
<td>additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg.</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Initial Dose: 4 Mg Orally Once A Day.</td>
<td>Usual maintenance dose ranges from 32 to 56 mg/day in two to four divided doses. dose is increased gradually every weeks over 6-8 weeks.</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Initially, 25 Mg At Night For 1 Wk, Thereafter Increase In Steps Of 25–50 Mg At Intervals Of 1–2 Wk</td>
<td>Doses &gt;25 mg/day should be taken in 2 divided doses. usual dose: 100-400 mg daily. max: 400 mg daily</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>50 Mg/Day In 2 Divided Doses, Up To 100 Mg/Day After 1 Wk.</td>
<td>May further dose increase at wkly intervals in steps of up to 100 mg. usual dose: 300-500 mg/day.</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Initial Dose: 50 Mg Twice Daily (100 Mg Per Day).</td>
<td>can be increased at weekly intervals by 100 mg/day given as two divided doses up to the recommended maintenance dose of 200 to 400 mg/day.</td>
</tr>
<tr>
<td>Rufinamide (For Lennox-Gastaut Syndrome)</td>
<td>Initial Dose: 400 To 800 Mg/Day Administered In Two Equally Divided Doses.</td>
<td>the dose should be increased by 400 to 800 mg/day every 2 days until a maximum daily dose of 3200 mg/day, administered in two equally divided doses is reached.</td>
</tr>
<tr>
<td>Vigabatrin (Seizure Prophylaxis)</td>
<td>Initial Dose: 1 G/Day (Administered As One 500 Mg Tablet Orally Twice Daily) With Or Without Food.</td>
<td>the total daily dose may be increased in 500 mg increments at weekly intervals depending on response. recommended dose: 3 g/day (1.5 g twice daily)</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Adjunctive Therapy: 1200 Mg/Day In 3-4 Divided Doses.</td>
<td>maximum daily dose: 3600 mg.</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Initial Dose: 600 Mg/Day, (Given As 300 Mg Twice A Day).</td>
<td>the recommended daily dose is 1200 mg/day.</td>
</tr>
<tr>
<td>Eslicarbazepinacetate (BIA 2-093)</td>
<td>400mg Once Daily For One To Two Weeks Then 800mg Once Daily.</td>
<td>based on individual response The dose may be increased to 1,200mg once daily.</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Loading Dose: 10 To 20 Mg Of Phenytoin Sodium Equivalents/Kg Iv At A Rate Of 100 To 150 Mg/Min.</td>
<td>Maximum dose 2,000 mg; maintenance dose: 4 to 6 mg/kg/day iv in 3 to 4 divided doses.</td>
</tr>
<tr>
<td>Stiripentol</td>
<td>50 Mg/Kg Per Day.</td>
<td>Increased up to 100 mg/kg per day, with a maximum of 4g. The dose to be divided into two or three with meals.</td>
</tr>
</tbody>
</table>

This mechanism of action is unique among antiepileptic drugs, and may hold promise for the treatment of other neurolologic conditions, including migraine and neuropathic pain. The adverse effects found in the Phase II trial mainly affected the central nervous system, and appeared to be dose-related. The most common adverse effects were drowsiness, dizziness and vertigo, confusion, and slurred speech. Less common side effects included tremor, memory loss, gait disturbances, and double vision.24, 25, 26

Psychiatric symptoms and difficulty urinating have also been reported, with most cases occurring in the first 2 months of treatment. Concomitant use of retigabine and digoxin may increase serum concentration of the latter.
**BRIVARACETAM**

Brivaracetam is believed to act by binding to the ubiquitous synaptic vesicle protein SV2. Phase II clinical trials in adult patients with refractory partial seizures were promising.

**Seletracetam** has high-affinity stereo specific binding to synaptic vesicle glycoprotein 2A (SV2A). Its binding to N-type calcium channels and preventing influx of Ca²⁺ during high-voltage activation that is typical of epilepsy. 15

**VALROCEMIDE**

It can be used in refractory epilepsy patients and phase III trials were being planned. 9

**GANAXOLONE**

Ganaxolone (INN, also known as CCD-1042) is an anaesthetic related to the steroidallopregnanolone that has sedative, anxiolytics, and anticonvulsant effects. It is selective positive allosteric modulator of GABAₐ receptors. 8 Trials in adults with partial seizures and in infantile spasms have recently been completed. 32,33,34

**TALAMPANEL**

Talampanel (GYKI 537773; LY300164) is a drug which has been investigated for the treatment of epilepsy. Malignant gliomas and amyotrophic lateral sclerosis (ALS). As of May 2010, results from the trial for ALS have been found negative. Talampanel is not currently under development. It is a non-competitive antagonist of the AMPA receptor, a type of glutamate receptor in the central nervous system. 35

**Tonabersat**, a first-in-class neuronal gap junction modulator. Tonabersat has been tested in a variety of neurological conditions, including migraine and epilepsy. Some other agents like, 2-deoxy-glucose, ICA-105665, imepitoin, NAX 801-2, perampanel and other AMPA receptor antagonists, valnoctamide and its homologue sec-propylbutylacetamide (SPD), VX-765 and YK3089, KCNQ4 channel activator (BMS-204352), are being investigated for their role in treatment of various types of epilepsies.

Newer antiepileptic drugs may control seizures more effectively, but their significant potential for serious side effects requires a thorough knowledge of the drugs and careful consideration of the risks and benefits.

Despite the introduction of many second-generation antiepileptic drugs (AEDs) in the past 15 years, a third of patients with epilepsy remain refractory to available treatments, and newer and more effective therapies are needed. Although our understanding of the mechanisms of drug resistance is fragmented, novel AED targets have been identified, and models of refractory targets have been developed that can help to select candidate compounds for development. There are more than 20 compounds with potential antiepileptic activity in various stages of clinical development, and for many of these promising clinical trial results are already available. Several incentives justify further investment into the discovery of newer and more effective AEDs. Moreover, developments in clinical trial methodology enable easier completion of proof-of-concept studies, earlier definition of the therapeutic potential of candidate compounds, and more efficient completion of trials for various epilepsy indications

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