RECENT ADVANCES IN THE MANAGEMENT OF EPILEPSY

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Introduction

A *seizure* (from the Latin *sacire*, "to take possession of") is a paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons. *Epilepsy* describes a condition in which a person has *recurrent* seizures due to a chronic, underlying process. Epilepsy refers to a clinical phenomenon rather than a single disease entity, since there are many forms and causes of epilepsy[1].

Epilepsy is the most common serious neurological disorder and is one of the world's most prevalent noncommunicable diseases. As the understanding of its physical and social burden has increased it has moved higher up the world health agenda. Over four-fifths of the 50 million people with epilepsy are thought to be in developing countries; much of this condition results from preventable causes. Around 90% of people with epilepsy in developing countries are not receiving appropriate treatment. Consequently, people with epilepsy continue to be stigmatized and have a lower quality of life than people with other chronic illnesses. However, bridging the treatment gap and reducing the burden of epilepsy is not straightforward and faces many constraints. Cultural attitudes, a lack of prioritization, poor health system infrastructure, and inadequate supplies of antiepileptic drugs all conspire to hinder appropriate treatment[1].

Epidemiology of epilepsy in developing countries[12]

The reported prevalence rates of active epilepsy in developing countries range from 5 to 10 per 1000 people. Reliable incidence figures are harder to establish because prospective studies have to contend with difficult and often insurmountable logistical problems concerning accurate case ascertainment. However, the more stringent studies have found annual incidence rates of up to 190 per 100 000 people in developing countries and of 50–70 per 100 000 people in industrialized countries[2].

Types of seizures [10,11,12]

1. Partial seizures

a. Simple partial seizures (with motor, sensory, autonomic, or psychic signs)

b. Complex partial seizures

c. Partial seizures with secondary generalization

2. Primarily generalized seizures

a. Absence (petit mal)

b. Tonic-clonic (grand mal)

c. Tonic

d. Atonic

e. Myoclonic

3. Unclassified seizures

a. Neonatal seizures

b. Infantile spasms

Existing antiseizure drugs provide adequate seizure control in about two thirds of patients. So-called "drug resistance" may be observed from the onset of attempted therapy or may develop after a period of relatively successful therapy. Explanations are being sought in terms of impaired access of the drugs to target sites or insensitivity of target molecules to them. In children, some severe seizure syndromes associated with progressive brain damage are very difficult to treat. In adults, some focal seizures are refractory to medications. Some, particularly in the temporal lobe, are amenable to surgical resection. Some of the drug-resistant population may respond to vagus nerve stimulation (VNS), a nonpharmacologic treatment for epilepsy now widely approved for treatment of patients with partial seizures. VNS is indicated for refractory cases or for patients in whom antiseizure drugs are poorly tolerated. Stimulating electrodes are implanted on the left vagus nerve, and the pacemaker is implanted in the chest wall or axilla. Use of this device may permit seizure control with lower doses of drugs[3].

New antiseizure drugs are being sought not only by the screening tests noted above but also by more focused approaches. Compounds are sought that act by one of three mechanisms: (1) enhancement of GABAergic (inhibitory) transmission, (2) diminution of excitatory (usually glutamatergic) transmission, or (3) modification of ionic conductances[2].

Although it is widely recognized that current antiseizure drugs are palliative rather than curative.

Mechanism of action of anti-epileptic drugs:

1)*Delaying the recovery from inactivation of* Na^+ *channels*- Phenytoin, Carbamazepine, Lamotrigine, Topiramate.

2)*Decreasing low threshold calcium currents (T-current) in the thalamic neurons*- Ethosuximaide, Valproate, Zonisamide.

3)*Facilitation of GABA mediated* Cl^- *channel opening*-

- Acting through GABA –related receptors: Barbiturates, Benzodiazepines.
- By releasing GABA from neuronal endings: Gabapentin
- By inhibiting GABA transaminase: Vigabetrin
- By inhibiting GABA reuptake: Tiagabin.

CLASSIFICATION[9]

Barbiturate- Phenobarbitone

Deoxybarbiturate- Primidone

Hydantoin- Phenytoin

Iminostilbine- Carbamazepine, Oxcarbamazepine

Succinimides- Ethosuximide

Aliphatic carboxylic acid- Valproic acid, Divalproex

Benzodiazepine- Diazepam, Lorazepam, Clobazem, Lamotrigine

Phenyltriazine- Lamotrigine

Cyclic GABA analogue- Gabapentin

Newer drugs- Vigabatrin, Topiramate, Tiagabine, Zonisamide, Levetiracetam.

General Pharmacokinetics of antiseizure medications[11]

The antiseizure drugs exhibit many similar pharmacokinetic properties—even those whose structural and chemical properties are quite diverse—because most have been selected for oral activity and all must enter the central nervous system. Although many of these compounds are only slightly soluble, absorption is usually good, with 80–100% of the dose reaching the circulation. Most antiseizure drugs (other than phenytoin and valproic acid) are not highly bound to plasma proteins.

Antiseizure drugs are cleared chiefly by hepatic mechanisms; although they have low extraction ratios. Many are converted to active metabolites that are also cleared by the liver. These drugs are predominantly distributed into total body water. Plasma clearance is relatively slow; many antiseizure drugs are therefore considered to be medium to long-acting. Some have half-lives longer than 12 hours. Many of the older antiseizure drugs are potent inducers of hepatic microsomal enzyme activity. Compliance is better with less frequent administration; thus extended-release formulations permitting once- or twice-daily administration may offer an advantage[3].

Established antiepileptics[7,9a,9b,13,]

DRUG	STARTING DAILY DOSE	INITIAL TARGET DOSE *mg/day*	BLOOD LEVEL *µg/ml*	COMMON SIDE EFFECTS	SERIOUS SIDE EFFECTS	OTHER CONSIDERATIONS
Carbamazepine	200 mg; increase daily dose by 200 mg every 3 days	400–600	4–12	Dizziness, diplopia, blurred vision, ataxia, sedation, weight gain, nausea, benign leukopenia*	Agranulocytosis (in approx 1/200,000 patients), aplastic anemia (in 1/500,000 patients) hepatic failure (very rare), rash (in approx 10% of patients), Stevens–Johnson syndrome (rare),† hyponatremia (in 1.8–40.0% of patients)	Monitor sodium, liver function tests, complete blood count; induces its own metabolism

Oxcarbazepine	300–600 mg; increase daily dose by 300–600 mg each wk	900–1200	3–40	Fatigue, dizziness, ataxia, diplopia, nausea, vomiting, headache	Rash; Stevens–Johnson syndrome or toxic epidermal necrolysis (0.5–6.0 cases per million patients), hyponatremia (serum sodium level, <125 mmol per liter) (in 2.5% of patients), anaphylaxis (rare)	10-monohydroxy metabolite is active component
Phenytoin	If initiated without titration, 3–5 mg/kg; may be initiated with a loading dose	200–300	10–20	Fatigue, dizziness, ataxia, diplopia, nausea, vomiting, confusion	Blood dyscrasias (rare), conduction block, pseudolymphoma, rash, Stevens–Johnson syndrome, or toxic epidermal necrolysis (in 2–4/10,000 patients), hepatic failure (rare), lupuslike syndrome	Nonlinear kinetics may lead to rapid increases in serum concentration with toxic effects after small changes in dose; gum hypertrophy, hirsutism may occur with long-term use; risk of osteopenia
Phenobarbital	30 mg; increase daily dose by 30 mg every 2 wk	60–120	15–45	Fatigue, dizziness, ataxia, diplopia, nausea, vomiting, confusion, depression, hyperactivity (in children)	Generally rare; blood dyscrasias, hepatic failure, rash,Stevens–Johnson syndrome or toxic epidermal necrolysis, arthritis	
Valproate valproic acid	250–500 mg, or 10–15 mg/kg orally once a day; increase daily dose by 250–500 mg each	750–2000	40–100	Drowsiness, ataxia, weight gain, nausea, vomiting, thrombocytopenia, tremor, hair loss	Hepatic failure (in 1/20,000 patients, higher rate among children and with polytherapy), hyperammonemia, aplastic anemia (rare), 1/3000 patients).	

Modern (newer)antiepileptic drugs:

1) Levetiracetam[36]:

Levetiracetam is the S-enantiomer of a-ethyl-2-oxo-1-pyrrolidineacetamide.

Pharmacological Effects And Mechanism Of Action :Levetiracetam exhibits clinical effectiveness against partial and secondarily generalized tonic-clonic seizures. The mechanism by which levetiracetam exerts these antiseizure effects is unknown.

Pharmacokinetics And Drug Interactions :Levetiracetam is rapidly and almost completely absorbed after oral administration and is not bound to plasma proteins. Ninetyfive percent of the drug and its inactive metabolite are excreted in the urine, 65% of which is unchanged drug; 24% of the drug is metabolized by hydrolysis of the acetamide group. Levetiracetam neither induces nor is a high-affinity substrate for CYPs or glucuronidases and thus does not interact with other antiseizure drugs, oral contraceptives, or anticoagulants.

Therapeutic Use &Toxicity **:**The addition of levetiracetam to other antiseizure medications in adults with refractory partial seizures improved control in one clinical trial. Insufficient evidence is available on use of levetiracetam as monotherapy for partial or generalized epilepsy. The drug is well tolerated; adverse effects include somnolence, asthenia, and dizziness.

2) Topiramate[38]:

Topiramate is a sulfamate-substituted monosaccharide.

Pharmacological Effects And Mechanisms Of Action**:** Topiramate reduces voltage-gated Na+ currents in cerebellar granule cells and may act in a manner similar to phenytoin. In addition, topiramate activates a hyperpolarizing K^+ current, enhances postsynaptic GABA-receptor currents, and also limits activation of the AMPA-kainate-subtype(s) of glutamate receptor. Topiramate also 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. Its $t_{1/2}$ is 1 day. Reduced plasma concentrations of estradiol occur with concurrent topiramate, suggesting that low-dose oral contraceptives should be avoided in this setting.

Therapeutic Use: Topiramate is equivalent to valproic acid and carbamazepine in children and adults with newly diagnosed partial and primary generalized epilepsy; the drug is also effective as monotherapy for refractory partial epilepsy and refractory generalized tonic-clonic seizures. Topiramate also is more effective than placebo against both drop attacks and tonic-clonic seizures in patients with Lennox-Gastaut syndrome.

Toxicity**:** Topiramate is well tolerated. Common adverse effects are somnolence, fatigue, weight loss, and nervousness. The drug can precipitate renal calculi (probably due to inhibition of carbonic anhydrase). Topiramate has been associated with cognitive impairment; patients may also complain about a change in the taste of carbonated beverages.

3) Tiagabine[37]:

Is a derivative of nipecotic acid.

Pharmacological Effects And Mechanism Of Action **:**Tiagabine inhibits the GABA transporter, GAT-1, and thereby reduces GABA uptake into neurons and glia. As a consequence, tiagabine prolongs the synaptic dwell time of GABA and increases the duration of synaptic inhibition.

Pharmacokinetics**:** Tiagabine is rapidly absorbed after oral administration, extensively bound to serum or plasma proteins, and metabolized in the liver by CYP3A. Its $t_{1/2}$ (8 hours) is shortened by 2–3 hours when the drug is coadministered with hepatic enzyme–inducers such as phenobarbital, phenytoin, or carbamazepine.

Therapeutic Use **:** Tiagabine is effective as add-on therapy of refractory partial seizures,with or without secondary generalization. Its efficacy as monotherapy for newly diagnosed or refractory partial and generalized epilepsy has not been established.

Toxicity: Adverse effects include dizziness, somnolence, and tremor, which are mild to moderate in severity and appear shortly after initiation of therapy. Tiagabine-enhanced effects of synaptically released GABA can facilitate spike-and-wave discharges in animal models of absence seizures, suggesting that tiagabine may be contraindicated in patients with generalized absence epilepsy; patients with a history of spike-and-wave discharges have been reported to have exacerbations of their EEG abnormalities.

4) Gabapentin & Pregabalin[14,15,16,42]:

Gabapentin is an amino acid, an analog of GABA, that is effective against partial seizures. Originally planned as a spasmolytic, it was found to be more effective as an antiseizure drug. Pregabalin is another GABA analog, closely related to gabapentin. This drug was recently approved in the USA for both antiseizure activity and for its analgesic properties.

Mechanism of Action: In spite of their close structural resemblance to GABA, gabapentin and pregabalin do not act directly on GABA receptors. They may, however, modify the synaptic or nonsynaptic release of GABA. An increase in brain GABA concentration is observed in patients receiving gabapentin. Gabapentin is transported into the brain by the L-amino acid transporter. Gabapentin and pregabalin bind avidly to the 2 subunit of voltage-gated Ca^{2+} channels. Gabapentin and pregabalin also act presynaptically to decrease the release of glutamate; this effect is probably dependent on reduced presynaptic entry of Ca^{2+} via voltage-activated channels.

Clinical Use & Dosage: Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures at dosages that range up to 2400 mg/d in controlled clinical trials. Open follow-on studies permitted dosages up to 4800 mg/d, but data are inconclusive on the effectiveness or tolerability of such doses. Monotherapy studies also document some efficacy. Some clinicians have found that very high dosages are needed to achieve improvement in seizure control. Effectiveness in other seizure types has not been well demonstrated. Gabapentin has also been found effective in the treatment of neuropathic pain and is now indicated for postherpetic neuralgia in adults at doses of 1800 mg and above. The most common adverse effects are somnolence, dizziness, ataxia, headache, and tremor.

Pregabalin is approved (as an adjunct) for the treatment of partial seizures, with or without secondary generalization; controlled clinical trials have documented its effectiveness. It is available only in oral form, and the daily dose ranges from 150 mg/d to 600 mg/d, usually in two or three divided administrations. Pregabalin is also approved for use in neuropathic pain, including painful diabetic peripheral neuropathy and postherpetic neuralgia.

Pharmacokinetics: Gabapentin is not metabolized and does not induce hepatic enzymes. Absorption is nonlinear and dose-dependent at very high doses, but otherwise the elimination kinetics are linear. The drug is not bound to plasma proteins. Drug-drug interactions are negligible. Elimination is via renal mechanisms; the drug is excreted unchanged. The half-life is short, ranging from 5 hours to 8 hours; the drug is typically administered two or three times per day.

Pregabalin, like gabapentin, is not metabolized and is almost entirely excreted unchanged in the urine. It is not bound to plasma proteins and has virtually no drug-drug interactions, again resembling the characteristics of gabapentin. Likewise, other drugs do not affect the pharmacokinetics of pregabalin. The half-life of pregabalin ranges from about 4.5 hours to 7.0 hours, thus requiring more than once-per-day dosing in most patients.

5) Vigabatrin[44]:

Current investigations that seek drugs to enhance the effects of GABA include efforts to find GABA agonists and prodrugs, GABA transaminase inhibitors, and GABA uptake inhibitors. Vigabatrin (-vinyl-GABA) is one of these drugs and has been registered in Canada, Europe, and South America.

Mechanism of Action: Vigabatrin is an irreversible inhibitor of GABA aminotransferase (GABA-T), the enzyme responsible for the degradation of GABA. It apparently acts by increasing the amount of GABA released at synaptic sites, thereby enhancing inhibitory effects. A decrease in brain glutamine synthetase activity is probably secondary to the increased GABA concentrations. It is effective in a wide range of seizure models. Vigabatrin is marketed as a racemate; the *S*(+) enantiomer is active and the *R*(–) enantiomer appears to be inactive.

Therapeutic Use**:** Vigabatrin is useful in the treatment of partial seizures and West's syndrome. The half-life is approximately 6–8 hours, but considerable evidence suggests that the pharmacodynamic activity of the drug is more prolonged and not well correlated with the plasma half-life. In adults, vigabatrin should be started at an oral dosage of 500 mg twice daily; a total of 2–3 g (rarely more) daily may be required for full effectiveness.

Toxicity**:** Typical toxicities include drowsiness, dizziness, and weight gain. Less common but more troublesome adverse reactions are agitation, confusion, and psychosis; preexisting mental illness is a relative contraindication. The drug was delayed in its worldwide introduction by the appearance in rats and dogs of a reversible intramyelinic edema; this phenomenon has not been observed in any patient to date. More recently, unfortunately, long-term therapy with vigabatrin has been associated with development of visual field defects in up to one third of patients. This adverse effect may not be reversible, and vigabatrin may therefore be relegated to use in patients—such as those with infantile spasms—who are refractory to other treatments.

6) Lamotrigine[39,40]:

Lamotrigine was developed as an antifolate agent, based on the model that reducing folate would combat seizures. The antiseizure effect of lamotrigine is unrelated to its antifolate properties.

Pharmacological Effects And Mechanisms Of Action :

Lamotrigine blocks sustained repetitive firing of neurons and delays recovery from inactivation of recombinant Na^+ channels, mechanisms similar to those of phenytoin and carbamazepine that may explain lamotrigine's actions on partial and secondarily generalized seizures. However, lamotrigine is effective against a broader spectrum of seizures than phenytoin and carbamazepine, suggesting additional actions that may include inhibiting synaptic release of glutamate.

Pharmacokinetics And Drug Interactions:

Lamotrigine is completely absorbed from the GI tract and is metabolized primarily by glucuronidation. The plasma $t_{1/2}$ of a single dose is 15–30 hours. Administration of phenytoin, carbamazepine, or phenobarbital reduces the $t_{1/2}$ and plasma concentrations of lamotrigine. Conversely, addition of valproic acid markedly increases plasma concentrations of lamotrigine, likely by inhibiting glucuronidation. Addition of lamotrigine to valproic acid produces a reduction of valproate concentrations by 25% over a few weeks. Concurrent use of lamotrigine and carbamazepine may be associated with increased levels of the 10,11-epoxide of carbamazepine and clinical toxicity.

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. Patients already taking antiseizure drugs that induce hepatic enzymes (e.g., carbamazepine, phenytoin, phenobarbital, or primidone) should be given lamotrigine initially at 50 mg/day for 2 weeks. The 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. For patients taking valproic acid in addition to an enzyme-inducing antiseizure drug, the initial dose should be 25 mg every other day for 2 weeks, followed by an increase to 25 mg/day for 2 weeks; the dose then can be increased by 25–50 mg/day every 1–2 weeks up to a maintenance dose of 100–150 mg/day divided into two doses.

Toxicity**:** Common adverse effects when lamotrigine is added to another antiseizure drug are dizziness, ataxia, blurred or double vision, nausea, vomiting, and rash. A few cases of Stevens-Johnson syndrome and disseminated intravascular coagulation have been reported. The incidence of serious rash in children (0.8%) is higher than in adults (0.3%).

7) Felbamate[43]:

Felbamate has been approved and marketed in the USA and in some European countries. Although it is effective in some patients with partial seizures, the drug causes aplastic anemia and severe hepatitis at unexpectedly high rates and has been relegated to the status of a third-line drug for refractory cases.

Mechanisms Of Action: Felbamate appears to have multiple mechanisms of action. It produces a use-dependent block of the NMDA receptor, with selectivity for the NR1-2B subtype. It also potentiates $GABA_A$ receptor responses. Felbamate has a half-life of 20 hours (somewhat shorter when administered with either phenytoin or carbamazepine) and is metabolized by hydroxylation and conjugation; a significant percentage of the drug is excreted unchanged in the urine. When added to treatment with other antiseizure drugs, felbamate increases plasma phenytoin and valproic acid levels but decreases levels of carbamazepine.

In spite of the seriousness of the adverse effects, thousands of patients worldwide remain on the medication. Usual dosages are 2000–4000 mg/d in adults, and effective plasma levels range from 30 mcg/mL to 100 mcg/mL. In addition to its usefulness in partial seizures, felbamate has proved effective against the seizures that occur in Lennox-Gastaut syndrome.

8) Oxcarbazepine[17,18,19]:

Oxcarbazepine is closely related to carbamazepine and useful in the same seizure types, but it may have an improved toxicity profile. Oxcarbazepine has a half-life of only 1–2 hours. Its activity, therefore, resides almost exclusively in the 10-hydroxy metabolite, to which it is rapidly converted and which has a half-life similar to that of carbamazepine, ie, 8–12 hours. The drug is mostly excreted as the glucuronide of the 10-hydroxy metabolite. Oxcarbazepine is less potent than carbamazepine, both in animal models of epilepsy and in epileptic patients; clinical doses of oxcarbazepine may need to be 50% higher than those of carbamazepine to obtain equivalent seizure control. Some studies report fewer hypersensitivity reactions to oxcarbazepine, and cross-reactivity with carbamazepine does not always occur. Furthermore, the drug appears to induce hepatic enzymes to a lesser extent than carbamazepine, minimizing drug interactions. Although hyponatremia may occur more commonly with oxcarbazepine than with carbamazepine, most adverse effects that occur with oxcarbazepine are similar in character to reactions reported with carbamazepine.

9) Zonisamide[27,28,29]:

Zonisamide is a sulfonamide derivative.

Pharmacological Effects And Mechanism Of Action **:**Zonisamide inhibits both the T-type Ca^{2+} currents and the sustained, repetitive firing of spinal cord neurons, presumably by prolonging the inactivated state of voltage-gated Na^+ channels in a manner similar to that of phenytoin and carbamazepine.

Pharmacokinetics: Zonisamide is almost completely absorbed after oral administration, has a long $t_{1/2}$ (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 the CYP3A4 metabolite, sulfamoylacetyl phenol. Phenobarbital, phenytoin, and carbamazepine decrease the plasma concentration/dose ratio of zonisamide, whereas lamotrigine increases this ratio. Zonisamide has little effect on the plasma concentrations of other antiseizure drugs.

Therapeutic Use: Clinical trials of patients with refractory partial seizures demonstrated that addition of zonisamide to other drugs was superior to placebo. Its efficacy as monotherapy for newly diagnosed or refractory epilepsy remains unproven.

Toxicity **:**Zonisamide is well tolerated. Adverse effects include somnolence, ataxia, anorexia, nervousness, and fatigue. Approximately 1% of individuals develop renal calculi during treatment with zonisamide, probably related to its ability to inhibit carbonic anhydrase.

Antiepileptic drugs in development[24,25,26]:

Ideally, the primary goal of AED research should be to develop novel compounds that are more effective in controlling seizures and/or are associated with fewer adverse effects compared with existing drugs. To achieve this goal, three main strategies are presently being pursued by researchers and the pharmaceutical industry, namely modification of the structures of existing drugs, development of compounds against novel drug targets and non-mechanism based screening of novel compounds.

Modification of existing drug[30,31,32]: Modification of the structures of existing drugs aims to discover compounds that have better effectiveness, reduced toxicity or improved pharmacokinetics.

a)Levetiracetam analogues: Brivaracetam and Seletracetam

b)Carbamazepine analogues: Eliscarbazepine acetate

c) Carbamates: Fluorofelbamate and Carisbamate

d)Valproate derivatives: Valpromide, Valrocemide and DP-VPA

* **Novel molecular targets:** These 'designer drugs' aim to target novel molecular substrates that are believed to be implicated in the pathogenesis of seizures.

Potassium channel opener:

1)Retigabine

2) AMPA(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor)antagonists: Talampanel, Becampanel and NS1209

3) Neuroactive steroids: Ganaxolone

Non-mechanism based screening: Some compounds have been developed by random screening using established animal models, many of which have subsequently been found to have novel structures or possess unknown mechanisms of action.

1) Lacosamide

2) Rufinamide

3) Safinamide:

4)Stiripentol:

GENERAL PRINCIPLES AND CHOICE OF DRUGS FOR THE THERAPY OF THE EPILEPSIES[4,5,6,]

Early diagnosis and treatment of seizure disorders with a single appropriate agent offers the best prospect of achieving prolonged seizure-free periods with the lowest risk of toxicity. A balancing of efficacy and unwanted effects in the individual patient provides the optimal therapeutic choice. The first consideration is whether to initiate treatment. For example, drug therapy may not be necessary after an isolated tonic-clonic seizure in a healthy young adult who lacks a family history of epilepsy and who has a normal neurological exam, EEG, and brain magnetic resonance imaging (MRI) scan—a setting where the risk of a drug reaction approximates the likelihood of seizure recurrence in the next year (15%). Alternatively, a similar seizure occurring in an individual with a positive family history of epilepsy, an abnormal neurological exam, an abnormal EEG, and an abnormal MRI carries a recurrence risk of 60% that favors initiation of therapy.

Unless extenuating circumstances exist (*e.g.,* status epilepticus), therapy should be initiated with a single drug, typically in dosage expected to provide a plasma concentration in the lower portion of the therapeutic range. To minimize dose-related adverse effects, therapy may be initiated at reduced dosage, increasing dosage at appropriate intervals, as required for control of seizures or as limited by toxicity, preferably assisted by monitoring of plasma drug concentrations. Faulty compliance is the most frequent cause for failure of therapy with antiseizure drugs; regularity of medication is essential. Compliance with a properly selected, single drug in maximal tolerated dosage results in complete control of seizures in 50% of patients. If a seizure occurs despite therapeutic drug levels, the physician should assess the presence of potential precipitating factor (*e.g.,* sleep deprivation, concurrent febrile illness, or drugs, including caffeine or over-the-counter medications). If compliance is confirmed yet seizures persist, another drug should be substituted. Unless serious adverse effects of the drug dictate otherwise, dosage always should be reduced gradually when a drug is discontinued to minimize risk of seizure recurrence. In the case of partial seizures in adults, the diversity of available drugs permits selection of a second drug that acts by a distinct mechanism.

In the event that therapy with a second single drug also is inadequate, many physicians resort to treatment with two drugs simultaneously. This decision should not be taken lightly, because most patients obtain optimal seizure control with fewest unwanted effects when taking a single drug. Nonetheless, some patients will not be controlled adequately without the simultaneous use of two or more antiseizure drugs. No properly controlled studies have systematically compared one particular drug combination with another, and the chances of complete control with this approach are not high. It seems wise to select two drugs that act by distinct mechanisms (*e.g.,* one that promotes Na+ channel inactivation, another that enhances GABA-mediated synaptic inhibition). Additional issues are the unwanted effects of each drug and the potential drug interactions. Many of these drugs induce expression of CYPs and thereby alter the metabolism of themselves and/or other drugs.

***Effective Plasma Levels of Six Antiseizure Drugs*[9a].**

Drug	Effective level (mcg/ml)	High effective level (mcg/ml)	Toxic level (mcg/ml)
Carbamazepine	4-12	7	>8
Primidone	5-15	10	>12
Phenytoin	10-20	18	>20
Phenobarbital	10-40	35	>40
Ethosuximide	50-100	80	>100
Valproate	50-100	80	>100

Drugs Used in Infantile Spasms[45]

The treatment of infantile spasms is unfortunately limited to improvement of control of the seizures rather than other features of the disorder, such as retardation. Most patients receive a course of intramuscular corticotropin, although prednisone may be equally effective and can be given orally. Clinical trials have been unable to settle the matter. In either case, therapy must often be discontinued because of adverse effects. If seizures recur, repeat courses of corticotropin or corticosteroids can be given, or other drugs may be tried. Other drugs widely used are the benzodiazepines such as clonazepam or nitrazepam; their efficacy in this heterogeneous syndrome may be nearly as good as that of corticosteroids. Vigabatrin is effective and is considered the drug of choice by many pediatric neurologists. The mechanism of action of corticosteroids or corticotropin in the treatment of infantile spasms is unknown but may involve reduction in inflammatory processes.

Status Epilepticus[46]

There are many forms of status epilepticus. The most common, generalized tonic-clonic status epilepticus is a life-threatening emergency, requiring immediate cardiovascular, respiratory, and metabolic management as well as pharmacologic therapy. The latter virtually always requires intravenous administration of antiseizure medications. Diazepam is the most effective drug in most patients for stopping the attacks and is given directly by intravenous push to a maximum total dose of 20–30 mg in adults. Intravenous diazepam may depress respiration (less frequently, cardiovascular function), and facilities for resuscitation must be immediately at hand during its administration. The effect of diazepam is not lasting, but the 30- to 40-minute seizure-free interval allows more definitive therapy to be initiated. Some physicians prefer lorazepam, which is equivalent to diazepam in effect and perhaps somewhat longer-acting. For patients who are not actually in the throes of a seizure, diazepam therapy can be omitted and the patient treated at once with a long-acting drug such as phenytoin.

Until the introduction of fosphenytoin, the mainstay of continuing therapy for status epilepticus was intravenous phenytoin, which is effective and nonsedating. It can be given as a loading dose of 13–

18 mg/kg in adults; the usual error is to give too little. Administration should be at a maximum rate of 50 mg/min. It is safest to give the drug directly by intravenous push, but it can also be diluted in saline; it precipitates rapidly in the presence of glucose. Careful monitoring of cardiac rhythm and blood pressure is necessary, especially in elderly people. At least part of the cardiotoxicity is from the propylene glycol in which the phenytoin is dissolved. Fosphenytoin, which is freely soluble in intravenous solutions without the need for propylene glycol or other solubilizing agents, is a safer parenteral agent. Because of its greater molecular weight, this prodrug is two thirds to three quarters as potent as phenytoin on a milligram basis.

In previously treated epileptic patients, the administration of a large loading dose of phenytoin may cause some dose-related toxicity such as ataxia. This is usually a relatively minor problem during the acute status episode and is easily alleviated by later adjustment of plasma levels.

For patients who do not respond to phenytoin, phenobarbital can be given in large doses: 100–200 mg intravenously to a total of 400–800 mg. Respiratory depression is a common complication, especially if benzodiazepines have already been given, and there should be no hesitation in instituting intubation and ventilation.

Although other drugs such as lidocaine have been recommended for the treatment of generalized tonic-clonic status epilepticus, general anesthesia is usually necessary in highly resistant cases.

For patients in absence status, benzodiazepines are still drugs of first choice. Rarely, intravenous valproate may be required.

Teratogenicity[44]

Epidemiological evidence suggests that anti-seizure drugs have teratogenic effects. These teratogenic effects add to the deleterious consequences of oral contraceptive failure. Infants of epileptic mothers are at 2-fold greater risk of major congenital malformations than offspring of non-epileptic mothers (4-8% compared to 2-4%). These malformations include congenital heart defects, neural tube defects, cleft lip, cleft palate, and others. Inferring causality from the associations found in large epidemiological studies with many uncontrolled variables can be hazardous, but a causal role for anti-seizure drugs is suggested by association of congenital defects with higher concentrations of a drug or with polytherapy compared to monotherapy. Phenytoin, carbamazepine, valproate, lamotrigine, and phenobarbital all have been associated with teratogenic effects. Newer anti-seizure drugs have teratogenic effects in animals but whether such effects occur in humans is yet uncertain. One consideration for a woman with epilepsy who wishes to become pregnant is a trial free of anti-seizure drug; monotherapy with careful attention to drug levels is another alternative. Polytherapy with toxic levels should be avoided. Folate supplementation (0.4 mg/day) has been recommended. Anti-seizure drugs that induce CYPs have been associated with vitamin K deficiency in the newborn, which can result in a coagulopathy and intracerebral hemorrhage. Treatment with vitamin K1, 10 mg/day during the last month of gestation, has been recommended for prophylaxis.

Withdrawal[41,48]

Withdrawal of antiseizure drugs, whether by accident or by design, can cause increased seizure frequency and severity. The two factors to consider are the effects of the withdrawal itself

and the need for continued drug suppression of seizures in the individual patient. In many patients, both factors must be considered. It is important to note, however, that the abrupt discontinuance of antiseizure drugs ordinarily does not cause seizures in nonepileptic patients, provided that the drug levels are not above the usual therapeutic range when the drug is stopped.

In general, withdrawal of anti-absence drugs is easier than withdrawal of drugs needed for partial or generalized tonic-clonic seizures. Barbiturates and benzodiazepines are the most difficult to discontinue; weeks or months may be required, with very gradual dosage decrements, to accomplish their complete outpatient removal. If a patient is seizure-free for 3 or 4 years, a trial of gradual discontinuance is often warranted.

Non pharmacological treatment

Ketogenic Diet[49]

The ketogenic diet was first advocated in 1921 after it was noted that ketosis and acidosis induced by a high fat-low carbohydrate diet had anticonvulsant effects similar to the effects of starvation. The treatment was rarely used once drugs became available to treat epilepsy. However, there has been a recent resurgence of interest in this treatment modality. The diet is initiated with starvation until ketones are present in the urine. This therapy should be initiated in a hospital because of the risk of development of hypoglycemia. The diet consists of very large amounts of fat, 1 g per kg per day of protein and minimal amounts of carbohydrates. A typical fat-to carbohydrate ratio is 4:1 or 3:1. A recent popular modification to the diet is the medium chain triglyceride variant. The diet is indicated for use primarily in young children with intractable symptomatic generalized epilepsy of the Lennox-Gastaut type, which is typically associated with diffuse brain abnormalities and some degree of mental retardation. Overall, 30 to 50 percent of children respond favorably. Those who respond show dramatic improvement, with at least a 50 percent reduction in seizure frequency within two to three weeks. The diet is typically maintained for two years. Some evidence suggests that it also may be effective in adults. While the ketogenic diet does not have the sedative and cognitive effects of antiepileptic drugs, there are some potential concerns regarding its effects on growth in children and on serum cholesterol levels in adults.

Vagus Nerve Stimulation[48]

Vagus nerve stimulation (VNS) is an entirely new treatment modality that has been extensively studied. VNS has an advantage over other electrical stimulations that have been investigated (e.g., cerebellar, thalamic) in that it does not require craniotomy. The mechanism of action is unclear, but it is likely mediated by the widespread afferent connections of the vagal nerve (which terminates in the nucleus of the solitary tract). The Neuro Cybernetic Prosthesis (Cyberonics, Inc., Houston) was labeled by the U.S. Food and Drug Administration in 1997 for adjunct treatment of partial epilepsy. It consists of two components: an electrode attached to the left vagus nerve through an incision in the neck and a generator, similar to a pacemaker that is surgically implanted in the chest wall. Efficacy is comparable to adjunctive antiepileptic drugs (a mean seizure frequency reduction of 25 to 35 percent and a seizure frequency reduction of at least 50 percent in 40 percent of patients). Furthermore, efficacy may increase over time. Unlike medications, VNS has no significant neurocognitive or systemic toxicity. The only common side effect is hoarseness of the voice or a mild cough on stimulation. Experience with this new treatment

modality is gradually increasing. Like the newer antiepileptic drugs, VNS is being investigated for use in conditions other than epilepsy, and trials for its use in the treatment of depression are ongoing.

Surgery[47]

Seizures are intractable in approximately 20 percent of patients with epilepsy. Consequently, it is estimated that the number of surgeries performed is well below the number of possible surgeries, despite the fact that surgery is now a well-accepted modality for the treatment of medically intractable epilepsy. The most common surgical procedures include anterior temporal lobe resection and hemispherectomies. Such surgery frequently results in complete seizure control, though the surgery is considered successful even if the patient requires AEDs to remain seizure-free.

ANTISEIZURE THERAPY AND PREGNANCY[50]

Antiseizure therapy has importance implications for women's health. The efficacy of oral contraceptives is reduced by concomitant use of antiseizure drugs (failure rate of 3.1/100 years versus 0.7/100 years in nonepileptic controls); this may relate to the increased rate of oral contraceptive metabolism caused by antiseizure drugs that induce hepatic enzymes; particular caution is needed with antiseizure drugs that induce CYP3A4. Infants of epileptic mothers are at twice the risk of major congenital malformations than offspring of nonepileptic mothers. These malformations include congenital heart defects and neural tube defects. A causal role for antiseizure drugs is suggested by association of congenital defects with higher concentrations of a drug or with polytherapy compared to monotherapy. Phenytoin, carbamazepine, valproate, and phenobarbital all have been associated with teratogenic effects.

The antiseizure drugs introduced after 1990 have teratogenic effects in animals but whether such effects occur in humans is uncertain. One consideration for a woman with epilepsy who wishes to become pregnant is a trial period without antiseizure medication; monotherapy with careful attention to drug levels is another alternative. Polytherapy with toxic levels should be avoided. Folate supplementation (0.4 mg/day) is recommended for all women of childbearing age to reduce the likelihood of neural tube defects, and this is appropriate for epileptic women as well. Antiseizure drugs that induce CYPs are associated with vitamin K deficiency in the newborn, possibly resulting in coagulopathy and intracerebral hemorrhage. Treatment of the mother with vitamin K1, 10 mg/day during the last 2–4 weeks of gestation, has been recommended for prophylaxis.

FUTURE DIRECTIONS[12,13]**:**

A recent trend in genetic studies of epilepsy has been the finding of gene mutations resulting in channelopathies. Mutations in genes encoding sodium channel subunits were found to underlie various epileptic syndromes of infancy, including generalized epilepsy with febrile seizures plus (GEFS+), severe myoclonic epilepsy of infancy, and benign familial neonatal-infantile seizures. Genetic testing might also identify patients at risk for seizure recurrence,allowing more rapid initiation of treatment.

Choice Of Anti-Epileptic Drugs[46]

Type of seizure	1st DOC	2nd DOC	Alternative/add on drugs
Generalized tonic clonic /simple partial	Carbamazepine, phenytoin	Valproate, phenobarbitone	Lamotrigine, gabapentin, topiramate, primidone
Complex partial	Carbamazepine, valproate, phenytoin	gabapentin, Lamotrigine,	Clobazam,zonisamide, topiramate,tiagabin
Absence	Valproate	Ethosuximide,lamotrigine	Clobazam, clonazepam
Myoclonic	Valproate	Lamotrigine, topiramate	Clonazepam, primidone
Atonic	Valproate	Clobazam, clonazepam	Lamotrigine,
Febrile seizures	Diazepam(rectal)		
Status epilepticus	Diazepam(i.v) Lorazepam(i.v)	Fosphenytoin(i.v) Phenobarbitone(i.v/i.m)	General anaesthetics

Conclusion

Recent years have brought new tools for the diagnosis of epilepsy, with advances in MRI techniques, the advent of MEG, increased availability of PET and SPECT, and use of multimodal imaging studies such as EEG/fMRI. Minimally invasive means of intracranial EEG monitoring are more commonly employed, such as epidural pegs and foramen ovale electrodes. A wider range of treatment options also exists, including new anticonvulsants, dietary therapies, implantable devices, and earlier surgical interventions.

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