An Overview about Treatment Modalities of Epilepsy

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Abstract
For most people with epilepsy, antiseizure medications are the main treatment modality, with the aim of stopping seizures at the earliest opportunity without causing side effects, which can affect quality of life. Seizure remission is also likely to reduce morbidity and to decrease the risk of premature mortality associated with continuing seizures, particularly motor seizures. The outlook for most patients with newly diagnosed epilepsy is good; around 65% to 70% achieve long-term seizure freedom with the first or second antiepileptic drug prescribed. However, despite the availability of more than 22 antiepileptic drugs, it is estimated that around 30% of newly diagnosed epilepsy patients will remain resistant to both drug monotherapy and polytherapy and will continue to experience seizures. Many drugs can be used for focal and generalized seizures. Others are specific for particular forms of seizures, for example sodium channel modulators are mainly appropriate for focal seizures. For those who might require treatment, an individualized management plan needs to be put in place promptly.

Keywords: Seizures, management, epilepsy

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Introduction

Epilepsy is one of the most common brain conditions, affecting almost 70 million people across the world. It is characterized by a lasting tendency to develop spontaneous epileptic seizures and has many neurobiological, cognitive, and psychosocial consequences **(1)**.

The pathophysiology of epilepsy or epileptogenicity occur due to alterations of normal physiological processes, which lead to synchronous and sustained firing of a population of neurons in the brain. Altered excitatory and inhibitory influences predispose to excessive synchrony within neuronal populations. The behavioral manifestations of a seizure reflect the function of the cortical neurons involved in the generation and spread of abnormal electrical activity **(2)**.

Three key elements contribute to the development of the hyperexcitability needed for epileptogenesis: 1) the capability of membrane in pacemaker neurons to develop intrinsic burst discharges; 2) the reduction of gamma-amino-butyric acid (GABA) inhibition; and 3) enhancement of synaptic excitation through recurrent excitatory circuits (mossy fiber sprouting in hippocampal sclerosis). Although intrinsic membrane hyperexcitability provides a substrate for

epileptogenesis, circuit dynamics are more important for paroxysmal electrophysiological tendencies **(3)**.

1. Kindling Phenomenon:

The observation that normal neurons can become epileptogenic by repeated stimulation, a process termed kindling, has provided a model for the study of the development of complex partial seizures. Kindling refers to a process by which brief trains of subconvulsive electrical stimuli are repeatedly delivered at appropriate intervals to a susceptible area of the brain. When stimulations are continued for even longer periods, spontaneous seizures appear. Once established, the effects of kindling are permanent. Kindling also can be achieved by chemical stimulation of cortex **(4).**

The resulting recurrent excitatory connections have been implicated in the progressive development of hyper-synchronous discharge. During kindling, the efferent from the granule cells of the dentate gyrus called "mossy fiber pathway" undergoes reorganization of the synaptic connections. Such synaptic reorganization is associated with loss of pyramidal cells, and has been demonstrated in human epileptic tissue **(5).**

2. Ionic channelopathies:

Ion channel dysfunction is widely speculated as a potential etiology for epilepsy. The neuronal cytoplasmic membrane consists of a lipid bilayer that is largely impermeable to ions, however ions can be actively transported across the membrane by pumps and can move through voltage-gated or ligand-gated channels depending on their electrochemical gradients. The ionic pumps create and maintain the resting membrane potential, whereas the ionic currents flowing through the gated channels lead to changes in the excitation state **(6)**.

Reduction in extracellular space induces seizure like activity that is independent of chemical synaptic mechanisms. The repetitive synaptic activation of cortical neurons and the intense synchronous activity during epileptic events are associated with an increase in extracellular potassium [K^+] and decrease in extracellular calcium [Ca^{2+}]. Increased K^+ was shown to induce inter-ictal spikes that lead to seizure activity. On the other hand, decrease in Ca^{2+} increases membrane excitability. These two phenomena, when they occur together, were shown to increase significantly the seizure susceptibility in hippocampus **(7)**.

Gaidin et al., (8) suggested that Ca^{2+} and magnesium [Mg^{2+}] interact with the neuronal membrane to cause inhibition of sodium [Na^+] movement, thus hypocalcaemia and hypomagnesaemia would be expected to cause an increase in Na^+ influx and depolarization.

3. Neurotransmission:

Excitatory neurotransmissions: in the brain are mediated largely by the excitatory amino acid “glutamic acic”. It is released from the presynaptic terminals and may bind to any of several glutamate receptors subtype. Kainate and "amino-3 hydroxy-5-methyl-isoxasole propionic acid" (AMPA) are selective agonists **(9).** The AMPA glutamate receptors are also termed non-NMDA receptors, while N-methyl-D-aspartate is a very selective agonist for another subtype of glutamate receptors (therefore, termed NMDA receptors). Glutamate is a flexible molecule that can bind to both NMDA and non-NMDA receptors, with different physiologic consequences in each case. Non-NMDA receptors mediate the fast excitatory neurotransmission giving an excitatory

postsynaptic potential (EPSP). Binding of glutamate to non-NMDA receptors cause influx of sodium ions [Na^+] through the receptor's pore producing a fast excitatory post synaptic potential (EPSP) often followed by an action potential **(10).**

The activation of metabotropic glutamate receptors (mGluRs) on astrocytes was shown to induce the release of glutamate through a calcium-dependent process. These results reveal a pathway of regulated transmitter release from astrocytes and outline the existence of an integrated glutamatergic cross-talk between neurons and astrocytes in situ that may play a critical role in epileptogenesis **(11).** Acetylcholine as well has a modulatory role in epilepsy through its muscarinic receptors. It acts as an excitatory neurotransmitter in cerebral cortex and limbic system, and these excitatory paths may well be involved in the propagation of seizures. In animals cholinergic agonists such as pilocarpine can cause severe seizures that may progress to status epilepticus and produce permanent neuronal loss and synaptic reorganization **(12).**

Inhibitory neurotransmission: The primary inhibitory transmitter in the brain is gamma-amino-butyric acid (GABA) which is synthesized from glutamate in the presynaptic terminal by action of the enzyme glutamic acid decarboxylase (GAD), which requires pyridoxine (vitamin B6) as a cofactor. Influx of Ca^{2+} caused by depolarization of the terminal prompts vesicles to release GAD into the synaptic cleft. Gamma-amino-butyric acid diffuses across the cleft and binds to its receptors (GABAa) which opens a pore or channel through which chloride ions [Cl^-] enter the neuron **(13).**

This Cl^- influx increases the negative charge inside the postsynaptic neuron, thereby hyperpolarizing it. The resultant change in membrane potential is called an inhibitory postsynaptic potential (IPSP) which reduces firing of the neuron by temporarily keeping the membrane potential away from firing threshold. Obviously, a reduction of any component of the GABA inhibitory postsynaptic potential system favors excitation and predisposes to epileptic firing. Conversely, enhancing the GABA system is a logical approach for restraining neuronal hyper excitability **(14).**

$GABA_b$ receptors are presynaptic or postsynaptic. $GABA_b$ receptor activation may result in different effects depending on their location. Activation of the $GABA_b$ receptor-linked K^+ channels results in prolonged hyperpolarization and leads to postsynaptic inhibition. On the other hand, the long duration of the $GABA_b$-mediated potentials may be responsible for some epileptic effects, as $GABA_b$ agonist, such as baclofen, are reported to exacerbate the spike-wave discharges in generalized epilepsies **(15).** The opposite effect for baclofen was found in another study as it suppressed generalized epilepsy and had antiepileptic effect **(16).**

Adenosine also is an endogenous neuromodulator with inhibitory effects on brain function. One of the most important actions of the adenosine receptor (mainly A1 receptor) is a reduction in excitatory transmission and in postsynaptic excitability. During seizures, brain adenosine concentrations rise markedly. This increase may play a role in the termination of seizures and may lead to the postictal depression of neural activity. Alterations in 5-hydroxytryptamine (5-HT) metabolism have been associated with myoclonic disorders **(17).**

Seizures resulting from pyridoxine deficiency are postulated to involve a reduction in brain GABA through decreasing the activity of its synaptic enzyme glutamic acid decarboxylase. A

disturbance of binding of the critical cofactor pyridoxal-5-phosphate (PLP) would thus be expected to cause a relative decrease of GABA **(18)**.

Treatment of epilepsy

Drug treatment

For most people with epilepsy, antiseizure medications are the main treatment modality, with the aim of stopping seizures at the earliest opportunity without causing side effects, which can affect quality of life. Seizure remission is also likely to reduce morbidity and to decrease the risk of premature mortality associated with continuing seizures, particularly motor seizures **(19).**

The outlook for most patients with newly diagnosed epilepsy is good; around 65% to 70% achieve long-term seizure freedom with the first or second antiepileptic drug prescribed. However, despite the availability of more than 22 antiepileptic drugs, it is estimated that around 30% of newly diagnosed epilepsy patients will remain resistant to both drug monotherapy and polytherapy and will continue to experience seizures **(20).**

Many drugs can be used for focal and generalized seizures. Others are specific for particular forms of seizures, for example sodium channel modulators are mainly appropriate for focal seizures. For those who might require treatment, an individualized management plan needs to be put in place promptly **{Table (1)} (21).**

Table (1): List of antiseizure medications by efficacy (21)

Focal and most generalized seizures	Benzodiazepines,lamotrigine,levetiracetam, perampanel,phenobarbital, topiramate, sodium valproate, zonisamide
Focal seizures only	Brivaracetam, carbamazepine, eslicarbazepine acetate, gabapentin, lacosamide, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin
Absence seizures only	Ethosuximide
Special encephalopathies only	Cannabidiol, everolimus, felbamate, rufinamide, stiripentol

In older people, who often are taking many concomitant drugs for comorbidities, medications with potential drug to drug interactions should be avoided where possible. An example of a positive association would be the choice of an antiseizure medication with antimigraine potential in someone with a history of migraine **(22).**

Medication choice is influenced by individual circumstances such as age, sex, child-bearing potential, comorbidities, and tolerability issues in one hand, and seizure type and epileptic syndrome in the other hand **{Figure (1)} (23).**

Drug-resistant epilepsy is assumed after the "failure of adequate trials of two tolerated, appropriately chosen and used antiseizure drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom". In those cases, it is a good practice to rule out all possibilities for treatment failure and to ensure that the diagnosis is correct **(24).**

Several issues need to be considered when selecting an appropriate drug and dosage for a given elderly individual including, changes in pharmacokinetic factors, routes of administration, drug interactions and adverse effect profiles of the given drug. Many physiological changes occur during aging that affect medication pharmacokinetics and result in a predisposition to adverse effects, for example, the absorption of drugs might be reduced or become erratic in older individuals **{Table (2)}** (25).

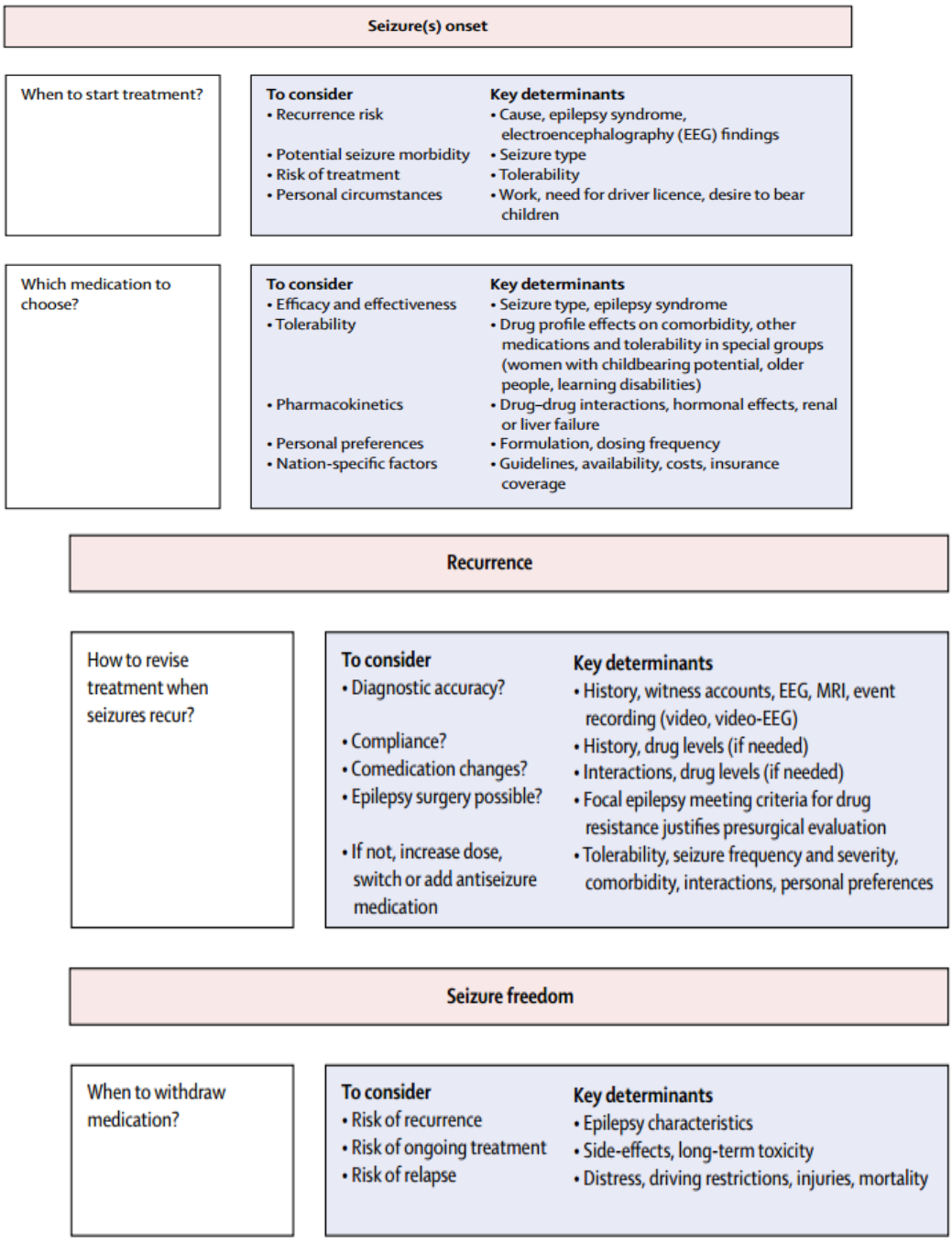

Figure (1): Key decisions in the pharmacological treatment of epilepsy **(23).**

Table (2): Pharmacokinetic changes in the elderly (25)

Process	Effect on Drug Disposition
Absorption	Possibly reduced intestinal absorption of agents requiring active transport Reduced first-pass metabolism Increased absorption of some high-clearance drugs Decreased absorption of drugs from prodrugs
Distribution	Altered free fraction of some drugs Increased free fraction of albumin-bound drugs Decreased free fraction of α 1-glycoprotein-bound drugs Altered volume of distribution Increased half-life for lipophilic drugs Increased permeability of blood-brain barrier
Metabolism	Delayed metabolism of high clearance drugs
Excretion	Increased half-life for water-soluble drugs

Progressive reduction in creatinine clearance and hepatic clearance have been observed with increasing age, resulting in higher serum antiepileptic drugs (AEDs) concentrations than in younger adults. The effect of decreased clearance tends to outweigh that of decreased absorption and the binding of drugs to serum proteins can be reduced with age because of decreased serum albumin levels resulting in an increased protein free fraction for drugs that are highly protein bound, such as phenytoin and valproate **(26).** Many elderly patients are receiving antihypertensives, anticoagulants, antiarrhythmic agents, lipid lowering medications, diuretics, and/or psychoactive medications at the time of diagnosis with epilepsy and the main interactions of concern are those owing to the effects of drugs on hepatic enzymes or through competition for protein binding **(22).**

Enzyme inducing antiepileptic medications can induce the metabolism of other concomitant medications; for example, carbamazepine and phenytoin can lower the serum concentration of simvastatin and reduce the efficacy of warfarin, enzyme inhibiting medications such as fluoxetine can increase carbamazepine (CBZ) levels **(27).**

Elderly patients who are taking herbal supplements which affect cytochrome P450 enzyme systems and others such as star anise and ginkgo biloba might increase the risk of seizures because of their intrinsic pro-convulsant properties **(28).** Elderly patients are at an increased risk of osteopenia and osteoporosis, which can lead to pathological fractures. Enzyme inducing antiepileptic drugs (AEDs) are expected to reduce vitamin D levels and increase bone turnover. However, long term treatment with AEDs leads to reduced bone mineral density irrespective of enzyme inducing capabilities and the risk of hip fractures was shown to be increased by the use of these drugs, especially in women **(29).**

Noncompliance is a major issue in elderly patients, particularly in the case of medications prescribed to treat multiple chronic disorders, such as epilepsy, coronary artery

diseases or osteoporosis. Noncompliance was associated with more than a threefold increase in risk of mortality, as well as a markedly higher incidence of emergency room visits so, measures to improve AEDs compliance are particularly important in elderly patients with multiple medical problems **(30).**

Surgical treatment

People with drug resistant epilepsy might benefit from removal or disconnection of a circumscribed brain region to achieve full seizure control, or at least stop disabling seizures. The proportion of individuals that are seizure-free after surgery ranges from 50–80% in well selected groups. Surgery seems cost effective and better than the best medical treatment in terms of seizure control and quality of life. Benefits of successful surgery also include reduced risk of injury or premature death, opportunity to drive, greater independence and perhaps improved vocational options **(31).**

Surgical treatment is, however, still underused and potential candidates are often not referred or are referred late, possibly because of misconceptions and fears (such as, ambiguous view on pharmaco-resistance, ignorance of surgical options, negative views on chances of achieving seizure freedom, fear of risks, and of surgery related personality changes). Few resources or little expertise is also a barrier in less wealthy countries, and might be counteracted by raising public awareness and the establishment of regional epilepsy centers **(32).**

Neuromodulation

Neurostimulatory techniques are palliative options when surgery is not possible or if surgery failed. Electrical pulses are applied to peripheral nerves or specific brain areas in response to enhanced rhythmicity to counteract potential seizure generation or propagation. The stimulatory pulses can be delivered in a scheduled manner (open-loop) or in response to seizures (closed-loop) **(33).**

Scheduled stimulation of the vagus nerve reduces seizure frequency by 50% or more in about a third of the patients, improves quality of life, and might decrease Sudden Unexpected Death in Epilepsy (SUDEP) risk **(19).** Advanced technology allows application of additional pulses triggered by seizure-related increases of heart rate, which might alleviate seizure severity. Deep brain stimulation of the thalamus reduces seizures by more than 50% in about half of the patients and might decrease SUDEP risk **(34).**

A new approach is to deliver electrical pulses directly to a seizure focus in response to enhanced rhythmicity, changes in frequency, or amplitude of the electroencephalogram (EEG) signals related to seizure generation (responsive neurostimulation) by implanted intracranial electrodes placed according to the results of preceding invasive pre-surgical evaluation **(19).** This treatment improves seizure control by more than 50% in about half of the patients and might decrease SUDEP risk. Antiseizure efficacy seems to increase over time in all neurostimulatory techniques **(34).**

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