SEIZURES

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Membrane potential

- Membrane potentials are always expressed as intracellular relative to extracellular potential.
- Resting membrane potential is primarily determined by K^+.
- When K^+diffuses from intracellular to extracellular fluid down its concentration gradient, the inner membrane potential becomes negative relative to the outer membrane potential.
- The Na^+-K^+ pump is responsible for maintaining the K^+ concentration gradient that is responsible for the resting membrane potential.

Membrane potential

- Cl^- moves down its concentration gradient (extracellular fluid to intracellular fluid).
- However, as chloride ion moves against an electrical gradient (on the Na^+-K^+-Cl^- co-transporter), energy is required to move Cl^-.
- Low extracellular Ca^{2+} levels alter the resting potential.
- 3 Na^+ are pumped out for every 2 K^+ (or 1 Ca^{2+}) pumped in.

Action potential

- The nerve action potential consists of a transient self-propagated reversal of charge on the membrane.
- When Na^+ channels open, Na^+ diffuses down its concentration gradient (outside to inside). An action potential is generated. At the peak of the upstroke, the inner membrane potential becomes positive relative to the outer membrane potential.
- (The internal potential goes from a negative value, through zero potential, to a slightly positive value primarily through increases in Na^+ permeability and then returns to resting values by an increase in K^+ permeability.)

Action potential

- The Na^+/K^+ pump (Na^+/K^+-ATPase) tends to extrude Na^+ from the interior of the cell, but it carries K^+ ions inward.
- The Na^+-K^+ pump is responsible for maintaining the Na^+concentration gradient that is responsible for the upstroke.
- Activation of voltage-dependent Ca^{2+} channels contributes to the depolarizing phase.
- Depolarization opens K^+ channels, resulting in outward movement of K^+, repolarization, closure of the Na^+ channel, and hyperpolarization.

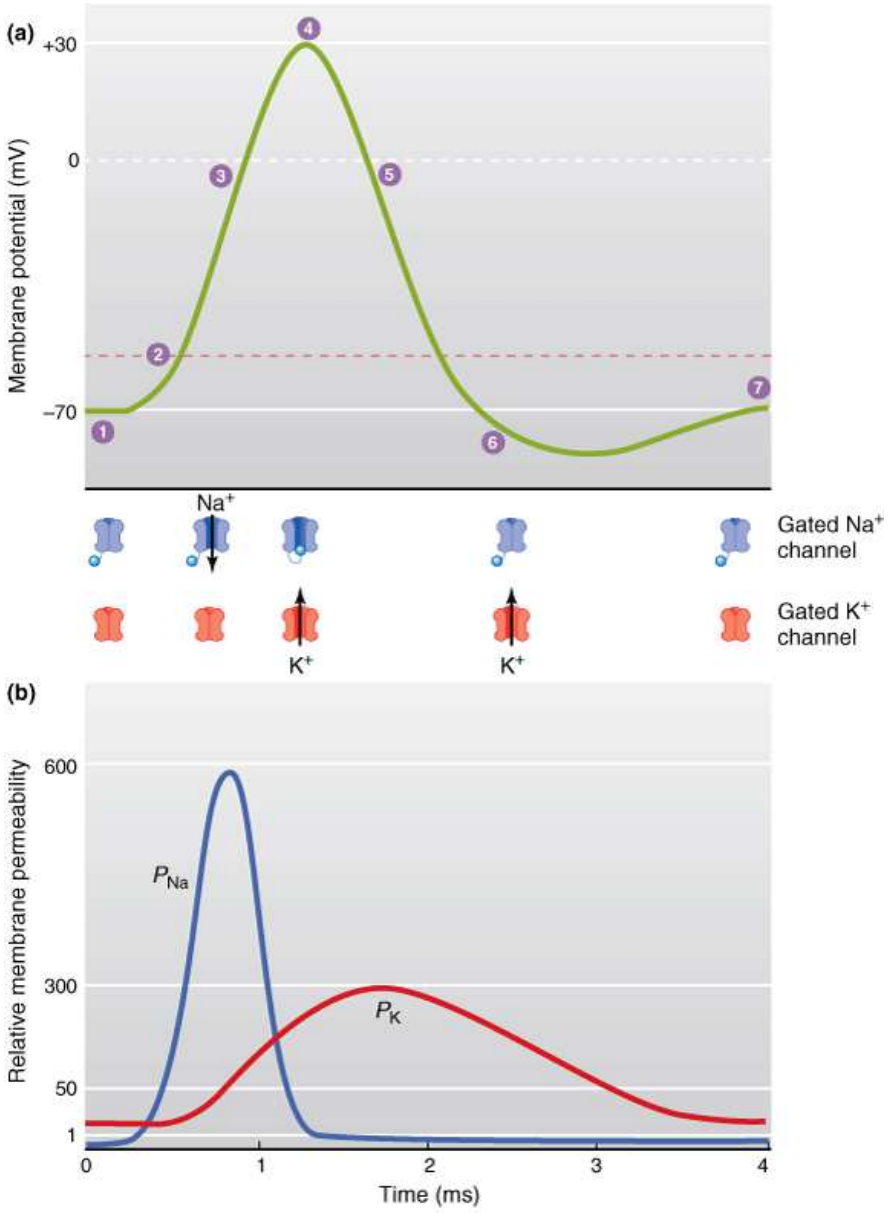
Action potential

- A depolarizing current pulse directly activates a series of unitary action potentials for as long as the input remains above the threshold; this is the tonic mode of firing.
- When the action potential arrives at the pre-synaptic terminal, it initiates release of the excitatory or inhibitory transmitter. Depolarization at the nerve ending and entry of Ca^{2+} initiate docking and then fusion of the synaptic vesicle with the membrane of the nerve ending.

Chronicity

- Neuronal circuits are internally modulated by feedback loops.
- Neurons either fire or do not fire. Synapses either permit transmission or they do not. The mutual interaction of neuronal fibers (or network) is summed and interpreted as perception.

Action potential



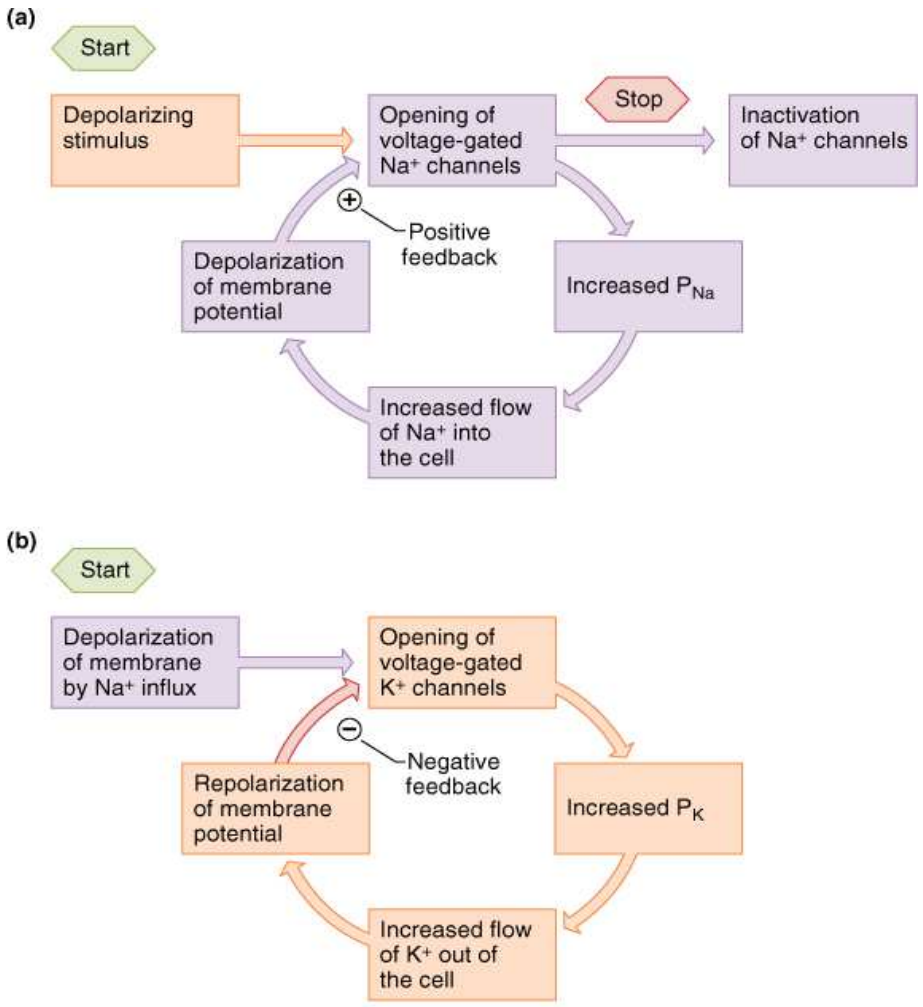
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

The changes in (a) membrane potential (mV) and (b) relative membrane permeability (P) to Na+ and K+ during an action potential.

(From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Fig. 4-6 Accessed 03/01/2010

Feedback control



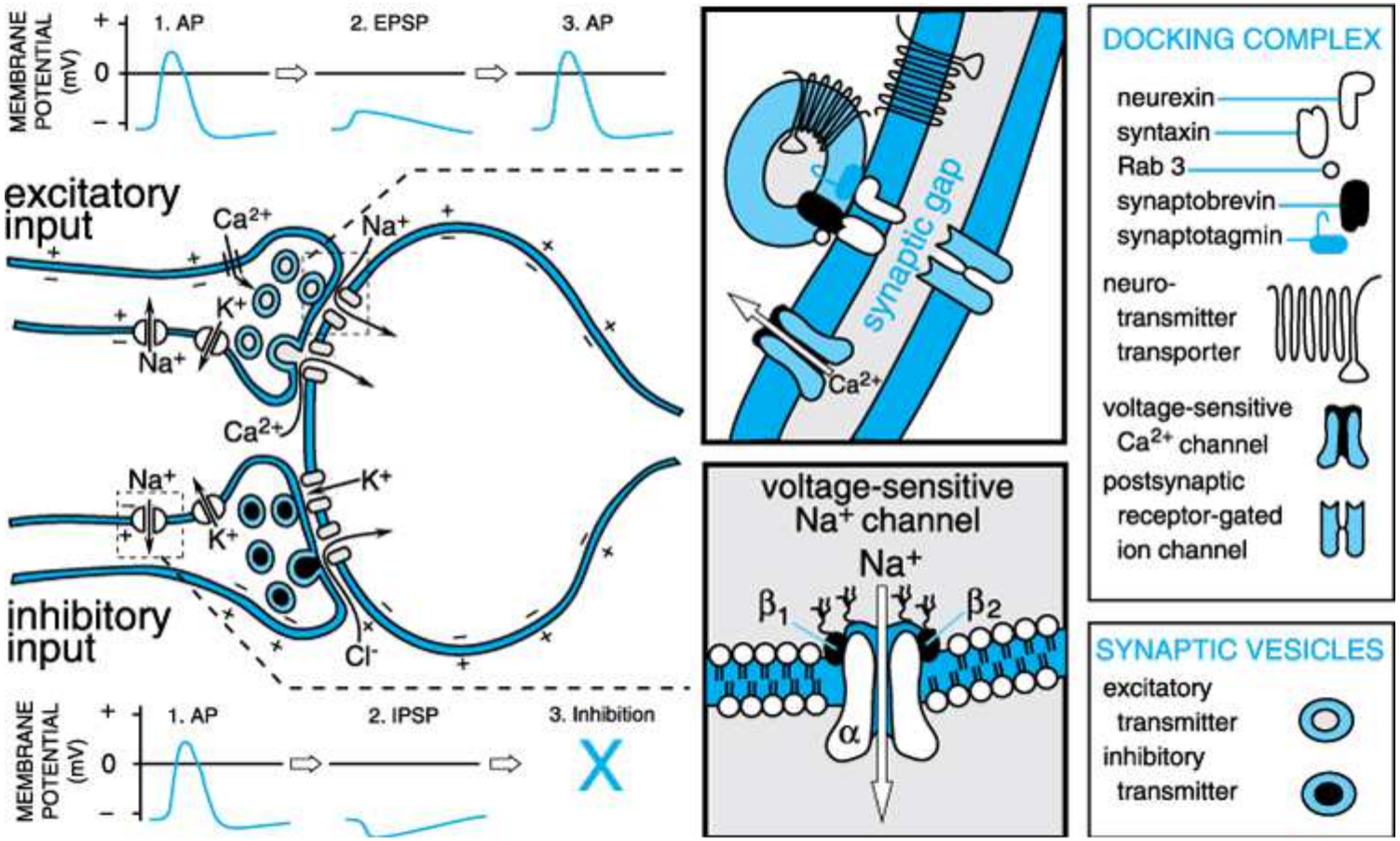
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(a) Na^+ channels exert positive feedback. **(b)** K^+ channels exert negative feedback.

(From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Fig. 4-7 Accessed 03/01/2010

Synapse



(Modified from Eccles, 1964, 1973; Katz, 1966; Catterall, 1992; Jahn and Südohorf, 1994.)

Fig. 6-2 Accessed 02/01/2010

Pre-synaptic inhibition

- Pre-synaptic inhibition is a mechanism that permits the "gain" at a particular synaptic input to be reduced without reducing the efficacy of other synapses that impinge on that neuron.
- The reduction in neurotransmitter is caused either by a decrease in the size of the action potential in the pre-synaptic terminal as a result of activation of K^+ or Cl^- channels or by reduced opening of Ca^{2+} channels in the pre-synaptic terminal, thereby decreasing the amount of transmitter release.

Pre-synaptic inhibition

- Binding of neurotransmitters to the receptors mediating pre-synaptic inhibition leads to a reduction in the amount of neurotransmitter secreted by the post-synaptic axon.
- Synaptic conduction can be strengthened or weakened on the basis of past experience.

Pre-synaptic inhibition

- Habituation is a simple form of learning in which a neutral stimulus is repeated many times.
- Non-associative learning.
- The first time it is applied it is novel and evokes a reaction. As it is repeated, the stimulus evokes lesser responses as intracellular Ca^{2+} is decreased as Ca^{2+} channels are deactivated. Release of neurotransmitter from the pre-synaptic terminal is decreased.

Enhanced post-synaptic potentiation

- Post-tetanic potentiation is the production of enhanced post-synaptic potentials in response to stimulation. This enhancement lasts up to 60 seconds and occurs after a brief (tetanizing) train of stimuli in the pre-synaptic neuron that causes Ca^{2+} to accumulate in the pre-synaptic neuron as the intracellular Ca^{2+} binding sites swamped.
- This involves a Na^{+}-K^{+} ligand gated channel.

Enhanced post-synaptic potentiation

- Long-term potentiation is a rapidly developing persistent enhancement of the postsynaptic potential response to pre-synaptic stimulation after a brief period of rapidly repeated stimulation of the pre-synaptic neuron.
- It is initiated by an increase in intracellular Ca^{2+} in the post-synaptic rather than the pre-synaptic neuron.
- It may persist for days.
- Associative learning.

Enhanced post-synaptic potentiation

- Sensitization is the prolonged occurrence of augmented post-synaptic responses after a stimulus to which one has become habituated is paired once or several times with a noxious stimulus.
- Pre-synaptic facilitation may occur. Sensitization is due to a Ca^{2+}-mediated change in adenylyl cyclase that leads to a greater production of cAMP.

Enhanced post-synaptic potentiation

- Long-term depression is the opposite of long term potentiation. It is characterized by a decrease in synaptic strength and is produced by slower stimulation of pre-synaptic neurons (with a smaller rise in intracellular Ca^{2+}).
- Phosphorylation of the Glu_{R2} subunit of the AMPA receptors is required. Glutamate neurotransmission.
- It may be involved in the mechanism by which learning occurs in the cerebellum.

Post-synaptic inhibition

- Binding of excitatory neurotransmitter with post-synaptic receptors initiates a conducted action potential in the post-synaptic neuron (the excitatory post-synaptic potential) through the opening of Na^+ or Cl^- channels or the closing of K^+ channels. This produces depolarization.
- This can be prevented, however, by the hyper-polarization induced by a concurrent inhibitory post-synaptic potential.

Enhanced post-synaptic potentiaion

- The inhibitory transmitter causes a selective increase in permeability to Ca^{2+} or Cl^{-}, resulting in a localized hyper-polarization, the inhibitory post-synaptic potential. Glycine facilitates.
- The NMDA receptor-linked Ca^{2+} channels open only when both sets of synapses are activated. Thus, these synapses sense the "pairing" of two synaptic inputs. Mg^{2+} blocks these channels.
- As a result of increased Ca^{2+} admitted into post-synaptic cells by this mechanism, protein kinases are activated and alter the synapse so as to strengthen it. Memory formation occurs.

Electrical synapses

- 3-4nm between pre and post synaptic membrane bridged by gap junctions.
- Pre and post ganglion cytoplasm are continuous.
- Open after engagement by neurotransmitter.
- Signals transmitted by ions.
- No synaptic delay.
- Ion/electrical conduction may occur in either direction.

Chemical synapses

- 40nm wide synaptic cleft.
- Interact with G proteins
- Signal transmitted by chemicals
- 1-5ms synaptic delay across cleft.
- Usually unidirectional

Neurotransmitters

- Acetylcholine is found from basal forebrain to cortex; motor neurons to neuromuscular junction; interneurons in striatum.
- Subtypes M_1, N excitatory; subtype M_2 inhibitory
- Dopamine is found in substantia nigra to striatum, to limbic system.
- Subtypes D_1,D_2 inhibitory.
- GABA is found in cortical neurons, long projection pathways.
- Subtypes A,B inhibitory.

Neurotransmitters

- Glutamate is linked to ligand gated Ca^{2+} ion channel (Magnesium dependent). NMDA, ACPD, AMPA subtypes are excitatory.
- Glycine is found in the spinal cord. Inhibitory.
- Serotonin is found in the pontine raphe nuclei; medulla/pons to dorsal horn of spinal cord.
- Subtypes $5HT_{2A, 3, 4}$ excitatory; subtype $5HT_{1A}$ inhibitory. cAMP as second messenger.
- Norepinephrine is found in the locus ceruleus to limbic system; medulla to locus ceruleus, spinal cord. Subtypes α_1, β_1 excitatory; subtypes α_2, β_2 inhibitory.

Neurotransmitter receptors

Type	G-protein	Second messenger
N-N, N-M		Open Na^+, K^+ channels
M_1, M3	q	Increase IP3, DAG, intracellular $Ca^{2}+$
M_2	i	Opens K^+ channel, inhibits adenyl cyclase
α_1	q	Increases IP3, DAG, intracellular $Ca^{2}+$
α_2	i	Decreases cAMP or decreases intracellular $Ca^{2}+$ or closes K^+ channels
β (all)	s	Stimulate adeny cyclase, increase cAMP
D_1	s	Stimulates adenyl cyclase, increases cAMP
D_2	i	Inhibits adenyl cyclase, opens K^+ channels
H_1	q	Increases IP3, DAG, intracellular $Ca^{2}+$
H_2	s	Stimulates adenyl cyclase, increases cAMP
V_1	q	Increases IP3, DAG, intracellular $Ca^{2}+$
V_2	s	Stimulates adenyl cyclase, increases cAMP

Channel or receptor function

Channel or receptor	Function
Voltage-gated Na^+ channel	Sub-threshold enhanced post synaptic potential; action potential up-stroke. May contribute to repetitive action potential firing in seizure.
Voltage-gated K^+ channel	Action potential down-stroke. May be associated with abnormal action potential repolarization
Ca^{2+}-dependent K^+ channel	Hyperpolarization following action potential; sets refractory period. Limits repetitive firing.
Voltage-gated Ca^{2+} channel	Transmitter release; carries depolarizing charge from dendrites to soma
Non-NMDA receptor (i.e., AMPA)	Fast enhanced post synaptic potential. May initiate synchronicity in seizures.

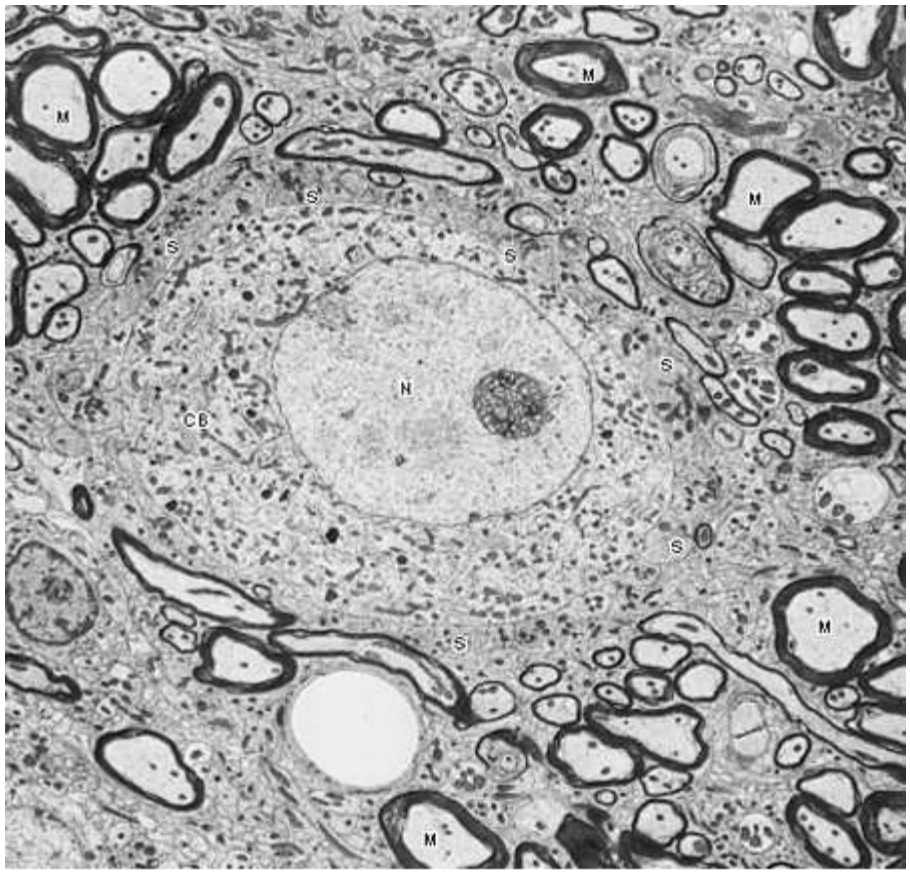
Channel or receptor functions

Channel or receptor	Function
NMDA receptor	Prolonged, slow excitatory post-synaptic potential. Maintains synchronous firing.
$GABA_A$ receptor	Inhibitory post-synaptic potential. Limits excitation.
$GABA_B$ receptor	Prolonged inhibitory post-synaptic potential. Limits excitation.
Electrical synapses	Ultra fast excitatory transmission permits synchronization of neuronal firing.
Na+-K+-ATPase pump	Restores ionic balance. Prevents K^+ induced depolarization in seizures.

Synapses

- Axo-somatic synapses terminate on neuronal cell bodies and tend to be inhibitory.
- Axo-dendritic synapses terminate on dendrities or mushroom-shaped "dendritic spines," and tend to be excitatory.
- Denditric-dendritic synapses may be excitatory or inhibitory.
- Axo-axonal synapses terminate on an axon, often close to synaptic terminals, and modulate the release of neurotransmitters (presynaptic inhibition).

Neuron



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*:
http://www.accessmedicine.com

The neuronal surface is completely covered by either synaptic endings of other neurons (S) or processes of glial cells. Many other processes around this cell are myelinated axons (M). CB, neuronal cell body; N, nucleus, x5000.

(Courtesy of Dr. DM McDonald.) Fig. 2-4 Accessed 02/01/2010

Synchronization

- The sustained firing during tonic mode means that the synapse is perpetually depressed, whereas bursts occur only after a requisite silence due to the hyper-polarization needed to de-inactivate the T Ca^{2+} channels.
- If the same cell is sufficiently hyperpolarized (for 100 msec), T Ca^{2+} channels are de-inactivated and primed for action. Now, the very same depolarizing pulse activates the low threshold Ca^{2+} spike; this is the burst mode of firing.

Synchronization

- Because tonic firing represents a direct link between an input depolarization, the larger the depolarization, the greater the response (in a linear fashion).
- Burst firing represents an indirect link between the input depolarization and action potential generation, the link being the low threshold Ca^{2+} spike.
- Because a larger depolarization does not evoke a larger low threshold Ca^{2+} spike, this input/output relationship is nonlinear, and approximates a step function.

Seizures

- Action potentials are normally generated in the opening of Na^+ channels and the inward movement of Na^+ down the intracellular concentration gradient (rapidly inactivating current).
- Activation of voltage-dependent Ca^{2+} channels contributes to the depolarizing phase.
- Depolarization opens K^+ channels, resulting in outward movement of K^+, repolarization, closure of the Na^+ channel, and hyperpolarization.
- Manifestations of ion channel abnormalities tend to be intermittent or paroxysmal.

Seizures

- Augmentation of non-inactivating (persistent) Na^+ current can augment cell depolarization and may promote burst firing in neurons.
- Ca^{2+} currents in hippocampal CA3 pyramidal cells underly burst discharges in these cells and may contribute to epileptic synchronization.
- Voltage dependent blockade of the NMDA receptor by Magnesium ion is reversed with depolarization. Activation of the NMDA receptor results in Ca^{2+} and Na^+ entry and generation of slow and long-lasting post synaptic potentials. Ca^{2+} entry also initiates second messenger pathways. These events contribute to burst discharges.

Seizures

- Non-NMDA ionotropic receptors are coupled to Na^+ and K^+channels. Activation of the post-synaptic receptor by glutamate is responsible for the fast-rising enhanced post-synaptic potentials (EPSP). The depolarization generated is necessary for effective activation of NDMA receptors.
- Glutamate receptors not coupled to ion channels are coupled to G-proteins.
- Inhibitor circuits utilize GABA as the neurotransmitter. Activation of $GABA_A$ receptors on the soma of a mature cortical neuron results in an influx of Cl^- (and HCO_3^-) and membrane hyperpolarization. (Immature neurons depolarize).

Seizures

- $GABA_A$ receptors are located on both the post-synaptic membrane and on pre-synaptic terminals. They control Ca^{2+} or K^+ conductance through G-proteins. They mediate long-lasting low-conductance inhibitory post-synaptic potentials (IPSP), primarily in the hippocampus. Activation of $GABA_B$ receptors on the presynaptic terminal blocks neurotransmitter release (and may disinhibit $GABA_A$ receptors).
- Glia restore ionic homeostasis (act as “sink”for K^+ release; regulate extracellular pH; remove gluatamate)

Seizure

- GABA transmission is labile. Intense discharges result in the failure of GABA response although interneuron function is intact. Breakdown of surround inhibition permits synchronization and seizure activity.
- Chronic stimulation of hippocampal inputs to the dentate gyrus or CA1 leads to hyperexcitability and seisure activity. Afterdischarge following initial stimulus becomes more extensive and prolonged with repeated stimuli (kindling process). Neuron death as terminal event of repeated stimulus. C-fos activated. GABAnergic neurons that contain Ca^{2+} binding proteins are spared (basket cells and axoaxonic neurons).

Seizures

- Initiated by two concurrent events:
- (1) High frequency bursts of action potentials.
- Caused by relatively long depolarization of the neuronal membrane leading to influx of extracellular Ca^{2+}, which leads to the opening of voltage dependent Na^{+} channels, allowing Na^{+} influx, and generation of repetitive action potentials.
- This is followed by a hyperpolarizing after-potential mediated by GABA receptors or K^{+} channels depending upon cell type.

Seizures

- (2) Hypersynchronization.
- Repetitive discharges lead to an increase in extracellular K^+, which blunts hyper-polarization and depolarizes neighboring neurons.
- Ca^{2+} ion accumulates in pre-synaptic terminals, leading to enhanced neurotransmitter release.
- Depolarization induced activation of the NMDA subtype of the excitatory glutamate receptor causes Ca^{2+} influx and neuronal activation.
- Neuronal recruitment and propagation follow.

Frontal lobe seizure

- Abrupt onset.
- May be simple or complex.
- May not show generalization.
- May not have long post-ictal phase.
- Often confused with hysteria.
- Characterized by adversive head movements and other complex actions such as swimming movements, genital activity, assuming a fencing posture.
- May see loss of speech or involuntary outcries, laughing, or staring.

Frontal lobe seizure

- May have associated mood changes.
- Autonomic dysfunction present.
- May occur frequently

Temporal lobe seizure

- Complex.
- May not generalize.
- There is post-ictal confusion.
- Characterized by hallucinations (may be gustatory, olfactory), compulsive thoughts, déjà vu, automatic movements (lip smacking, chewing as examples).

Parietal and occipital lobe seizures

- Both parietal lobe and occipital lobe seizures are simple.
- They may not generalize.
- There is no associated loss of consciousness.
- Parietal lobe seizures are characterized by sensory or motor phenomena.
- Occipital lobe seizures are characterized by unformed visual hallucinations.

Characteristics of partial seizures

Type	Signs
Simple	No loss of consciousness; seizures involve only sensory or motor systems
Complex	Impaired consciousness; onset localized, but spreads; involves limbic system; usually involves temporal lobe; may involve automatic movements (lip smacking, chewing as examples).
Myoclonic	No loss of consciousness. Very brief synchronized, bilateral jerks in arms and legs; may occur serially. 4-6Hz bilateral discharges on EEG.

Characteristics of generalized seizures

Type	Signs
Tonic-clonic (Grand mal)	Loss of consciousness; associated with generalized tonic muscle contractions (flexion: arms; extension: legs) followed by rhythmic contractions of limbs. May last minutes. Post-ictal phase can involve altered consciousness. 10-12Hz spikes on EEG .
Tonic	Loss of consciousness; rigid, violent muscle contractions; limbs fixed in abnormal positions
Clonic	Loss of consciousness; rhythmic muscle jerks; involves all parts of the body
Absence (Petit mal)	Brief loss of consciousness (vacant gaze followed by return to consciousness) May show automatic movements (lip smacking, chewing as examples). 3Hz bilateral discharges on EEG.
Atonic	Very brief loss of consciousness. Sudden loss of muscle tone (fall).

Seizure etiology

- A first seizure in someone younger than 40 should raise the suspicion of bacterial endocarditis.
- Febrile seizures commonly occur in those <5 years old. Does not itself predispose to seizure disorder.
- Neonates:
- Ischemia, hypoxia, trauma, metabolic (glucose, Calcium, Magnesium, pyridoxine), developmental, genetic
- Infants (1 month – 12 years of age)
- infection, trauma, genetic

Seizure etiology

- Adolescents (12-18 years of age)
- Trauma, infection, genetic, tumor, drugs
- Young Adults (18 – 35 years of age)
- Trauma, alcohol or drugs, tumor
- Adults (over 35 years of age)
- CVA, tumor, alcohol or drugs, metabolic, degenerative

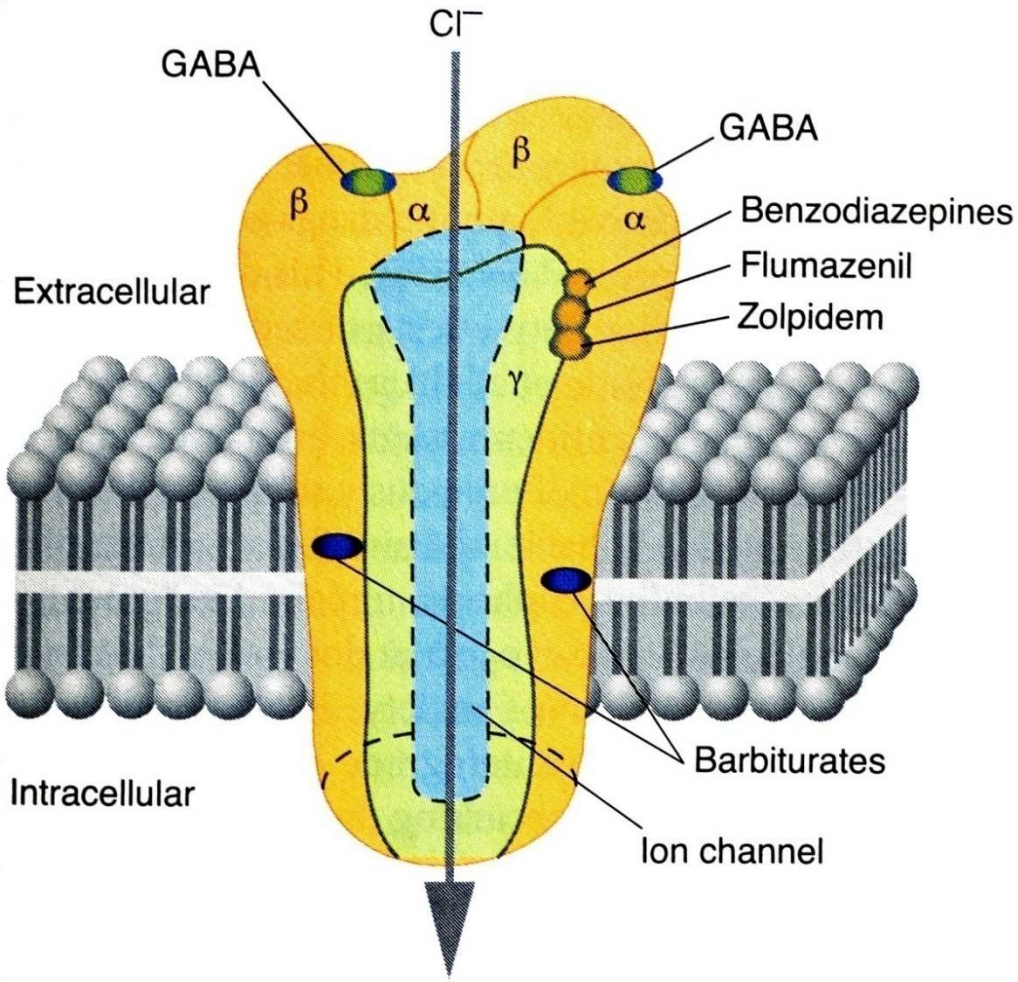
Anticonvulsant mechanisms

- Inhibition of Na^+ dependent action potentials in a frequency dependent manner:
- Phenytoin, carbamazepine, lamotrigine.
- Inhibition of voltage gated Ca^{2+} channels:
- Phenytoin.
- Inhibition of T-type Ca^{2+} ion channels (thalamus):
- Ethosuximide, valproic acid.
- Decrease glutamate release:
- Lamotrigine.
- Increase in availability of GABA:
- Valproic acid, gabapentin.

Anticonvulsant mechanisms

- Potentiation of GABA receptor function:
- Diazepam, barbiturates.
- Inhibition of presynaptic voltage gated N-type Ca^{2+} channel, blocking synaptic release of glutamate:
- Gabapentin, lamotrigine
- Inhibits burst firing by binding synaptic vesicle protein (SV2A) in hippocampus (inhibit Ca^{2+}currents), leading to diminished release of glutamate:
- Levatiracetam

$GABA_A$ Receptor Chloride channel



Anticonvulsant mechanisms

- GABA binds to α/β interface of $GABA_A$ receptor Cl^- channel
- Barbiturates bind along membrane; prolong Cl^- channel opening, potentiating GABA function
- Benzodiazepines bind to α/γ interface of $GABA_A$ receptor Cl^- channel opening; increase frequency of Cl^- channel opening, potentiating GABA function
- Valproic acid inhibits GABA transaminase, keeping Cl^- channel open, increasing availability of GABA
- <u>Only free drug is active. That is what should be measured.</u>

Anticonvulsants

Drug	Use	Toxicity and teratogenicity	Mechanism of Action
Phenytoin	Drug of choice for partial seizure Not indicated in porphyria	Nystagmus; ataxia; diplopia; hirsutism; gingival hyperplasia At high doses: sedation Cleft lip and palate	Inhibits voltage gated Na channels I neurons Zero order kinetics
Carbamazepine	Drug of choice for partial seizure Drug of choice for trigeminal neuralgia	Diplopia; ataxia Agranulocytosis; aplastic anemia in susceptible individuals Craniofacial defects Skin toxicity in those with HLAB*1501 mutation. SIADH	Enhancess voltage gated Na channel rapid inactivation and blocks L-type Ca channels in neurons
Valproic acid	Drug of choice for myoclonic seizures Absence seizures	Neural tube defects Hepatotoxic	Inhibits voltage gated Na channels and T-type Ca channels in neurons Inhibits GABA transaminase
Ethosuximide	Drug of choice for absence seizures	Stevens-Johnson syndrome	Blocks T-type Ca channels

Anticonvulsants

Drug	Use	Toxicity and teratogenecity	Mechanism of Action
Gabapentin	Focal-onset seizures Diabetic and post-herpetic neuralgia Restless leg syndrome	Sedation, ataxia	Binds pre-synaptic α-δ units of voltage gated Ca channels
Phenobarbital Primidone is metabolized to phenobarbital	Drug of choice for use in neonates Focal-onset, tonic-clonic seizures Essential tremor	Sedation, ataxia, confusion, rash	Binds synaptic and extra-synaptic $GABA_A$ receptors
Benzodiazepines	Drug of choice in status epilepticus Use after Magnesium sulfate in Eclampsia	Respiratory depression	GABA receptor agonist
Lamotrigine	Drug of choice in mood disorders of pregnancy Use in myoclonic seizures	Stevens-Johnson syndrome	Enhances voltage gated Na channel rapid inactivation and inhibits Ca channels in neurons
Topiramate	Migraine prophylaxis	Kidney stones	Inhibits voltage gated Na channels in neurons Inhibits GABA transaminase

Anticonvulsants

Drug	Use	Toxicity and teratogenecity	Mechanism of Action
Tiagabine	Partial seizures in those over 12 years of age	Confusion Do not use a loading dose	Inhibits GABA re-uptake into presynaptic neurons
Vigabatrin	Refractory complex partial seizures in those over 10 years of age who have failed other therapies	Vision loss	Inhibits GABA transaminase
Zonisamide	Focal onset seizures in adolescents Binge eating disorder	Sulfonamide	Suppresses neuronal hyper-synchronization by inhibiting Na voltage gated and T-type Ca channels
Clonazepam	Absence, myoclonic Seizures	Sedation, ataxia, anorexia	Allosteric modulator of GABA-A receptor
Levatiracetam	Partial onset seizures Myoclonic seizures Focal onset, tonic-clonic seizures Menstrual cycle related seizures	Somnolence, dizziness, asthenia, aggression, nasopharyngitis SIADH	Binds to synaptic vesicle protein SVA2

Acute seizure management

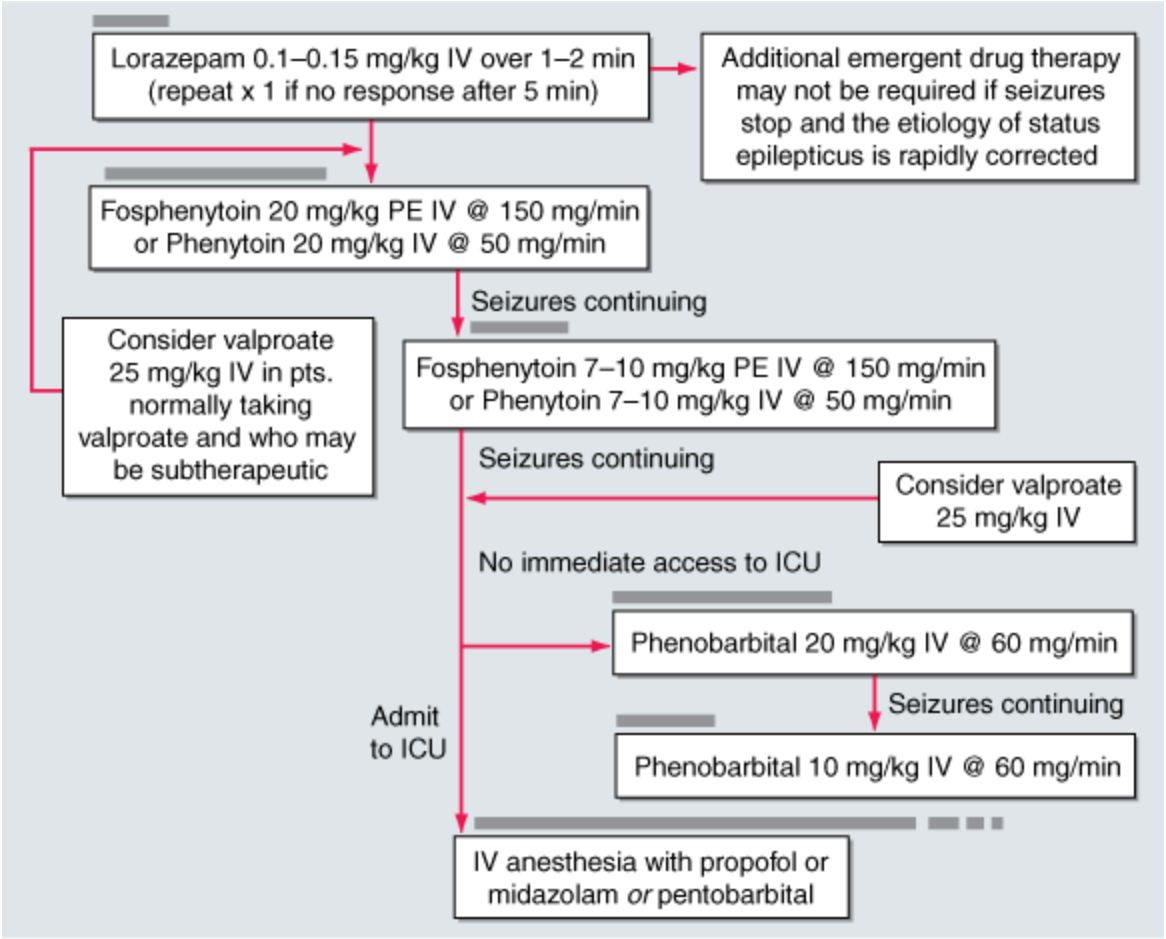


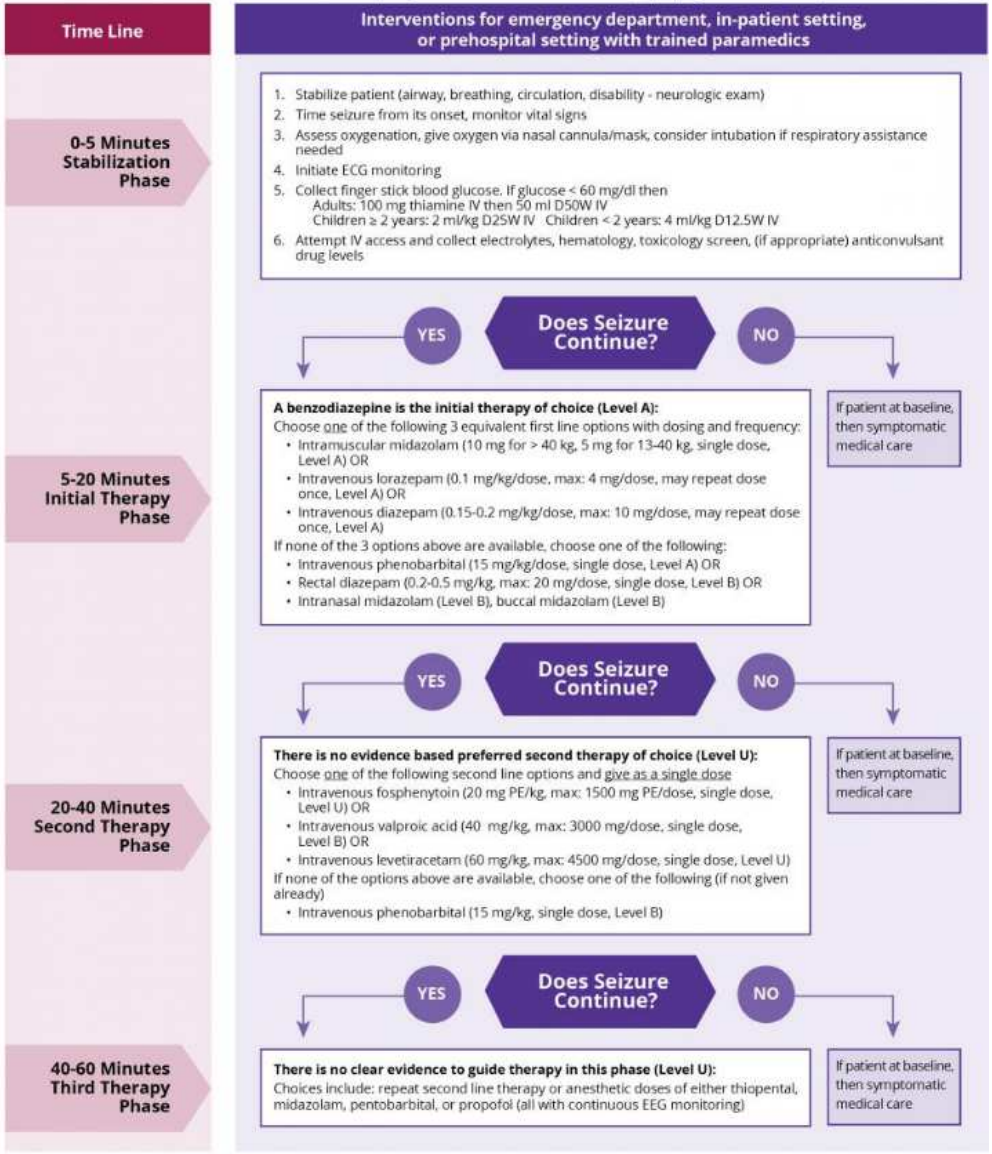
Fig. 363-3 Accessed 03/01/2010

Convulsive Status Epilepticus

- Diagnose if ≥ 5 minutes of sustained seizure activity with prominent motor symptoms and impairment of consciousness.
- Suspect nonconvulsive status epilepticus if coma and cessation of motor symptoms follow convulsive status epilepticus ("subtle" status epilepticus)
- Clinical presentations generally last ≥ 10-15 minutes
- Impaired consciousness of varying severity, or behavioral change, or sensory symptoms, or prolonged aura, or automatisms present

Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016



American Epilepsy Society

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

Seizure work-up

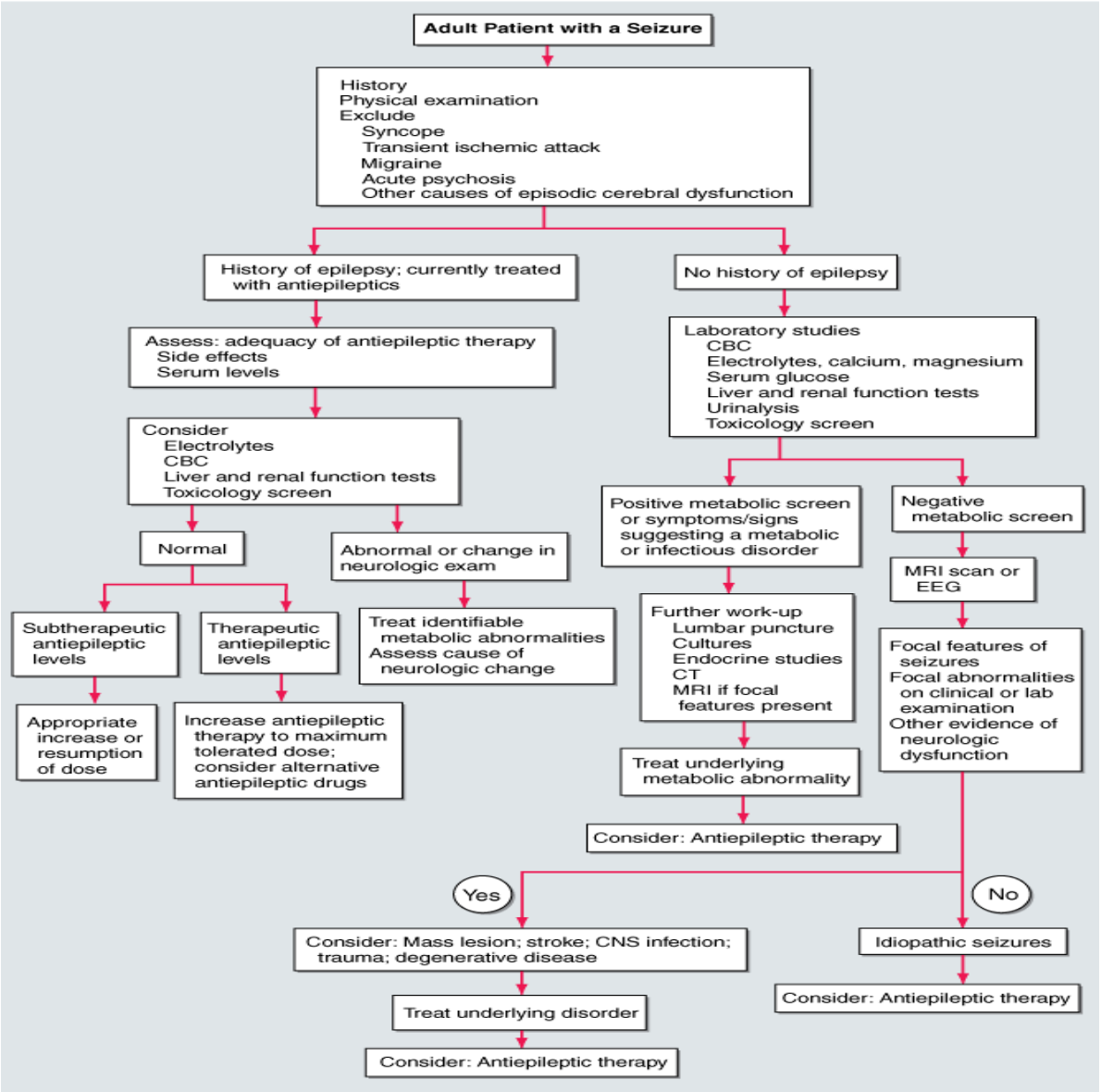


Fig. 363-2 Accessed 03/01/2010

Choice of seizure medications

- Valproate derivatives (including sodium valproate, valproic acid, and divalproex) should be avoided if possible in persons who may become pregnant.
- Focal epilepsy
- First line therapy is lamotrigine
- If poorly tolerated, carbamazepine or levetiracetam
- For drug-resistant focal epilepsy, consider adjunct antiseizure medications with any of carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, valproate, and zonisamide.

Choice of seizure medications

- For genetic generalized epilepsy or unclassified epilepsy
- First-line therapy is valproate.
- If poorly tolerated or inappropriate, lamotrigine or topiramate.
- Consider levetiracetam or lamotrigine in persons who may become pregnant.
- For drug-resistant generalized epilepsy, consider adjunct antiseizure medication use with any of lamotrigine, levetiracetam, ethosuximide, valproate, and topiramate.

Choice of seizure medications

- For provoked seizures (such as following acute brain insult, neurosurgery, or concussion), long-term antiseizure medication therapy is not indicated.
- Consider discontinuing antiseizure medication therapy in patients who are seizure-free for ≥ 2 years