Pharmacotherapy of headache

by Fasil.B

Introduction

- Headache is defined as diffuse pain in various parts of the head, with the pain not confined to the area of distribution of a nerve.
- Headache is among the most common pain problems encountered in family practice

Epidemiology

- Headache Is a Major Public Health Problem
- Up to 4% of ED Visits / 2% All Office Visits
- Over 20 Million Outpatient Visits
- 78 % of Women and 60% of Men Experienced at Least One Headache in the Year
- 36% of Women and 19% Men Suffered From Recurrent Headaches

classification

1.Primary headaches (recurrent, no organic disease):

- Migraine
- Tension-type headache and
- Cluster headache

2. Secondary headaches are caused by underlying organic diseases.

Acute Secondary Headache Disorders

1. Headache associated with head trauma
2. Headache associated with vascular disorders
   - SAH
   - Acute ischemic cerebrovascular disorder
   - Unruptured vascular malformation
   - Arteritis (e.g. temporal arteritis)
   - Arterial HTN

3. Headache associated with nonvascular intracranial disorder
- Benign intracranial HTN
- Intracranial infection
- Low CSF pressure

4 Headache associated with substance use or withdrawal

5. Headache associated with noncephalic infection (viral infection, bacterial infection)

6. Headache associated with metabolic disorder (hypoxia, hypercapnia, hypoglycemia, dialysis)

7. Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth or mouth

8. Cranial neuralgias pain

Migraine headache

☐A common, recurrent, primary headache of moderate to severe intensity, interferes with normal functioning and is associated with gastrointestinal (GI), neurologic, and autonomic symptoms.

- In migraine with aura, focal neurologic symptoms precede or accompany the attack

There are several types of migraine headache, but most are characterized by severe pain on one or both sides of the head (which may move to the other side), nausea, dizziness and visual disturbances caused by dilation and constriction of the blood vessels in the head

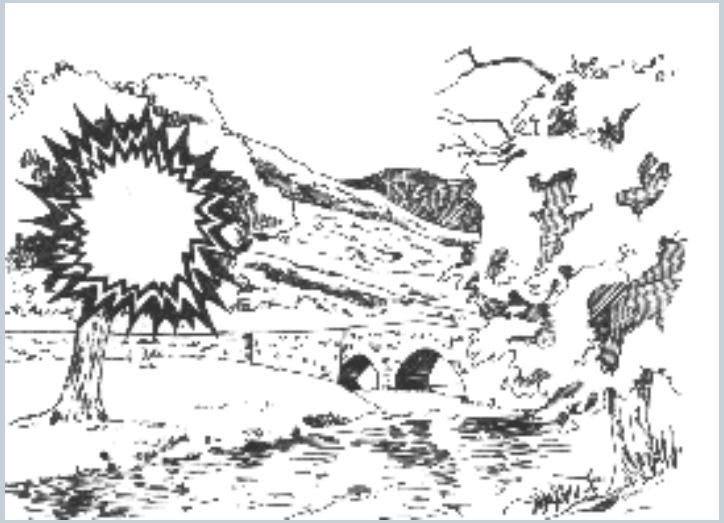
Pathophysiology of migraine

- Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide, neurokinin A, and substance P from perivascular axons.
- Vasodilation of dural blood vessels may occur with extravasation of dural plasma resulting in inflammation

CLINICAL PRESENTATION AND DIAGNOSIS

- Migraine headache is characterized by recurring episodes of throbbing head pain, frequently unilateral.
- Approximately 12% to 79% of migraineurs have premonitory symptoms in the hours or days before headache onset.
- Neurologic symptoms are most common
- but psychological
- autonomic and
- constitutional may also occur.

- A migraine aura is experienced by approximately 25% of migraineurs.
- Aura evolves over 5 to 20 minutes and lasts less than 60 minutes.
- Headache usually occurs within 60 minutes of the end of the aura.
- Visual auras can both
- positive features (eg photopsia, teichopsia, and fortification).
- and negative features (eg, scotoma and hemianopsia).
- Sensory and motor symptoms such as paresthesias or numbness of the arms and face, dysphasia or aphasia, weakness, and hemiparesis may also occur.



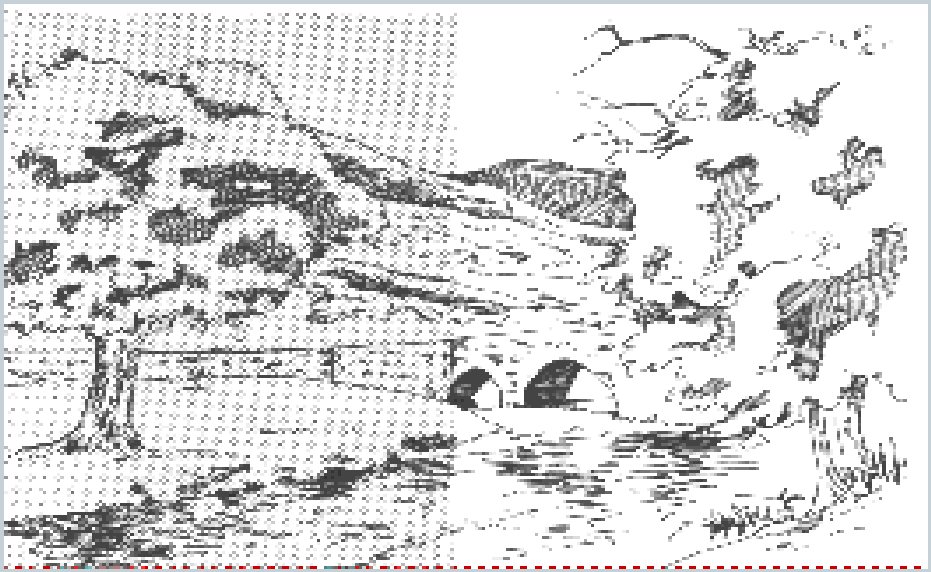


TABLE 447-3 SIMPLIFIED DIAGNOSTIC CRITERIA FOR MIGRAINE

Repeated attacks of headache lasting 4–72 h in patients with a normal physical examination, no other reasonable cause for the headache, and:

At Least 2 of the Following Features:	Plus at Least 1 of the Following Features:
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

Source: Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, 2013).

Treatment of migraine

Goal of therapy

- to achieve consistent, rapid headache relief with minimal adverse effects and symptom recurrence, and minimal disability and emotional distress.
- Limit use of acute migraine therapies to fewer than 10 days per month.

Nonpharmacological Treatment

- Apply ice to the head and recommend periods of rest or sleep, usually in a dark, quiet environment.
- Identify and avoid triggers of migraine attacks.
- Behavioral interventions (relaxation therapy, biofeedback, and cognitive therapy) may help patients who prefer nondrug therapy or when drug therapy is ineffective or not tolerated

Treatment: Goals of therapy

Short term

- Treat rapidly and consistently without recurrence
- Restore patient's ability to function
- Minimize use of backup and rescue medications
- Reduce cost and SE

Long term

- Reduce frequency, severity, and disability
- Improve quality of life
- Prevent headache
- Avoid escalation of headache medication use
- Educate and enable patients to manage their disease
- Reduce headache-related distress and psychological symptoms

TABLE 54–1	Commonly Reported Triggers of Migraine
Food triggers	
Alcohol	
Caffeine/caffeine withdrawal	
Chocolate	
Fermented and pickled foods	
Monosodium glutamate (e.g., in Chinese food, seasoned salt, and instant foods)	
Nitrate-containing foods (e.g., processed meats)	
Saccharin/aspartame (e.g., diet foods or diet sodas)	
Tyramine-containing foods	
Environmental triggers	
Glare or flickering lights	
High altitude	
Loud noises	
Strong smells and fumes	
Tobacco smoke	
Weather changes	
Behavioral–physiologic triggers	
Excess or insufficient sleep	
Fatigue	
Menstruation, menopause	
Sexual activity	
Skipped meals	
Strenuous physical activity (e.g., prolonged overexertion)	
Stress or post stress	

Pharmacologic Treatment of Acute Migraine

NSAIDs

- **Ergot alkaloids**
- Serotonin receptor agonists (**Triptans**)
- **Opioid** if the above drugs CI or not effective

Pharmacologic Treatment of Acute Migraine

- Administer acute migraine therapies at the onset of migraine.
- Pretreatment with an antiemetic (eg, **metoclopramide**, **chlorpromazine**, or **prochlorperazine**) 15 to 30 minutes before
- Frequent or excessive use of acute migraine medications can result in increasing headache frequency and drug consumption known as medication-overuse headache.
- Limit use of acute migraine therapies to 2 or 3 days per week.

Antiemetic's

- Prevent and treat nausea
- Improve GI motility
- Enhance absorption of other anti-migraine medications
- Limited RCT to support their use in migraine
- Dose metoclopramide 10 mg Po/iv Bid - Tid
- Promethazine 25-50 mg Q6hr
- Prochlorperazine 5-10 mg Q6hr

NSAIDs

- **Simple analgesics** and **NSAIDs** are first line treatments for mild to moderate migraine attacks; some severe attacks are also responsive.
- The combination of **acetaminophen**, **aspirin**, and **caffeine** is approved in the United States for relieving migraine pain.
- NSAIDs appear to prevent neurogenically mediated inflammation in the trigeminovascular system by inhibiting prostaglandin synthesis.

ERGOT ALKALOIDS AND DERIVATIVES

- are useful for moderate to severe migraine attacks.
- They are nonselective 5HT1 receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system.
- Venous and arterial constriction occurs.
- They also have activity at dopaminergic receptors.

- Contraindications to use of ergot derivative
  - renal and hepatic failure
  - coronary, cerebral
  - peripheral vascular disease
  - uncontrolled hypertension
  - Sepsis
  - and women who are pregnant or nursing.
- Oral and rectal preparations contain caffeine to enhance absorption and potentiate analgesia. Titrate to an effective dose that is not nauseating

- **SEROTONIN RECEPTOR AGONISTS (TRIPTANS)**
- Are appropriate first-line therapies for patients with mild to severe migraine or as rescue therapy when nonspecific medications are ineffective.
- They are selective agonists of the 5HT1B and 5HT1D receptors.

❖ Relief of migraine headache results from

(1)normalization of dilated intracranial arteries,

(2)Inhibition of vasoactive peptide release, and

(3)inhibition of transmission through second order neurons ascending to the thalamus.

- Lack of response to one triptan does not preclude effective therapy with another triptan.
- Side effects of triptans include paresthesias, fatigue, dizziness, flushing, warm sensations, and somnolence.
- Minor injection site reactions are reported with SC use, and taste perversion and nasal discomfort may occur with intranasal administration.

- Contraindications include ischemic heart disease, uncontrolled hypertension, cerebrovascular disease, hemiplegic and basilar migraine, and pregnancy.
- Do not give triptans within 24 hours of ergotamine derivative administration or within 2 weeks of therapy with monoamine oxidase inhibitors

TABLE 54–2 Dosing of Acute Migraine Therapies[a]

Drug	Dose
Analgesics	
Acetaminophen (Tylenol)	1,000 mg at onset; repeat every 4–6 hours as needed
Acetaminophen 250 mg/aspirin 250 mg/ caffeine 65 mg (Excedrin Migraine)	2 tablets at onset and every 6 hours
Nonsteroidal Antiinflammatory Drugs	
Aspirin	500–1,000 mg every 4–6 hours
Ibuprofen (Motrin)	200–800 mg every 6 hours
Naproxen sodium (Aleve, Anaprox)	550–825 mg at onset; can repeat 220 mg in 3–4 hours
Diclofenac (Cataflam, Voltaren)	50–100 mg at onset; can repeat 50 mg in 8 hours
Ergotamine Tartrate	
Oral tablet (1 mg) with caffeine 100 mg (Cafergot)	2 mg at onset; then 1–2 mg every 30 minutes as needed
Sublingual tablet (2 mg) (Ergomar)	
Rectal suppository (2 mg) with caffeine 100 mg (Cafergot, Migergot)	Insert 0.5 to 1 suppository at onset; repeat after 1 hour as needed

Dihydroergotamine	
Injection 1 mg/mL (D.H.E. 45)	0.25–1 mg at onset IM, IV, or subcutaneous; repeat every hour as needed
Nasal spray 4 mg/mL (Migranal)	One spray (0.5 mg) in each nostril at onset; repeat sequence 15 minutes later (total dose is 2 mg or four sprays)
Serotonin Agonists (Triptans)	
Sumatriptan (Imitrex)	
Injection	6 mg subcutaneous at onset; can repeat after 1 hour if needed
Oral tablets	25, 50, 85, or 100 mg at onset; can repeat after 2 hours if needed
Nasal spray	5, 10, or 20 mg at onset; can repeat after 2 hours if need
Zolmitriptan (Zomig, Zomig-ZMT)	
Oral tablets	2.5 or 5 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours if needed
Nasal spray	5 mg (one spray) at onset; can repeat after 2 hours if needed
Naratriptan (Amerge)	1 or 2.5 mg at onset; can repeat after 4 hours if needed

Prophylaxis (preventive)

- Consider prophylaxis in the setting of recurring migraines that produce significant disability
- frequent attacks requiring symptomatic medication more than twice per week;
- symptomatic therapies that are ineffective, contraindicated, or produce serious side effects

- Preventive therapy may also be given intermittently when headaches recur in a predictable pattern.
- Because efficacy of various prophylactic agents appears to be similar, drug selection is based on
  - side effect profiles and comorbid conditions.
- Response to an agent is unpredictable, and a 2- to 3-month trial is necessary to judge efficacy

- Only **propranolol**, **timolol**, **divalproex sodium**, and **topiramate** are FDA approved.
- Initiate prophylaxis with low doses, and advance slowly until a therapeutic effect is achieved or side effects become intolerable.
- Continue prophylaxis for at least 6 to 12 months after headache frequency and severity have diminished, and then gradual tapering or discontinuation may be reasonable.

Beta Blockers

- FDA approved for migraine prevention
- Propranolol 60-240 mg PO once daily for **ER** or divided BID or TID for IR
- Timolol 10-30 mg PO daily in 2 divided doses

- Advantages
- Thoroughly studied and widely used
- Timolol and propranolol are FDA approved
- Good choice for patients with HTN, CAD, tremor, or anxiety
- Disadvantages
- Side effects = fatigue, dizziness, depression, exercise intolerance, may worsen aura
- Avoid in patients with severe asthma, depression, bradycardia, Raynaud's, overt CHF

Calcium Channel Blockers

- Several trials have indicated some benefit for verapamil and flunarizine
- In recurrent migraine.

Verapamil in doses of 80 to 160 mg 3 times a day reduces the incidence of migraine with aura, but it is not as useful in migraine without aura

Tricyclic Antidepressants

- Amitriptyline 10-200 mg nightly
- Nortriptyline 10-150 mg nightly
- Desipramine 25-200 mg nightly
- Imipramine 10-200 mg nightly
- Doxepin 10-200 mg nightly
- Lower end of dosage range is usually effective for migraine prevention

- Advantages
  - Inexpensive
  - Once daily dosing
  - Good choice for patients with insomnia, neuropathy, mood disorders, fibromyalgia
- Disadvantages
  - None are FDA-approved
  - Side effects = sedation, weight gain, dry mouth, urinary retention
  - Avoid in sz disorder, cardiac conduction abnormalities, BPH

- Other Antidepressants
- ☐ Efficacy not established in clinical trials
- ☐ Best for fluoxetine 20 mg daily
- ☐ Anectodal evidence for other SSRIs, trazodone, mirtazapine, bupropion, venalfaxine, and duloxetine
- ☐ Migraines are more likely to be poorly controlled if mood disorders are untreated

NSAIDs

- Long-acting agents taken on a scheduled basis have low risk of causing MOH
- ❖ Consider for patients who:
- ✓ Have other chronic pain conditions
- ✓ Frequently use short-acting NSAID for acute treatment
- ✓ Are at low risk for developing complications from daily NSAID
- Caution patients about exceeding maximum daily dose
- Limited evidence to support efficacy

NSAIDs

- Diclofenac 75 mg PO BID
- Naproxen 500 mg PO BID
- Meloxicam 7.5-15 mg PO daily
- Celecoxib 200 mg PO daily
- Aspirin 81-325 mg PO daily
  - May be especially helpful for reducing aura

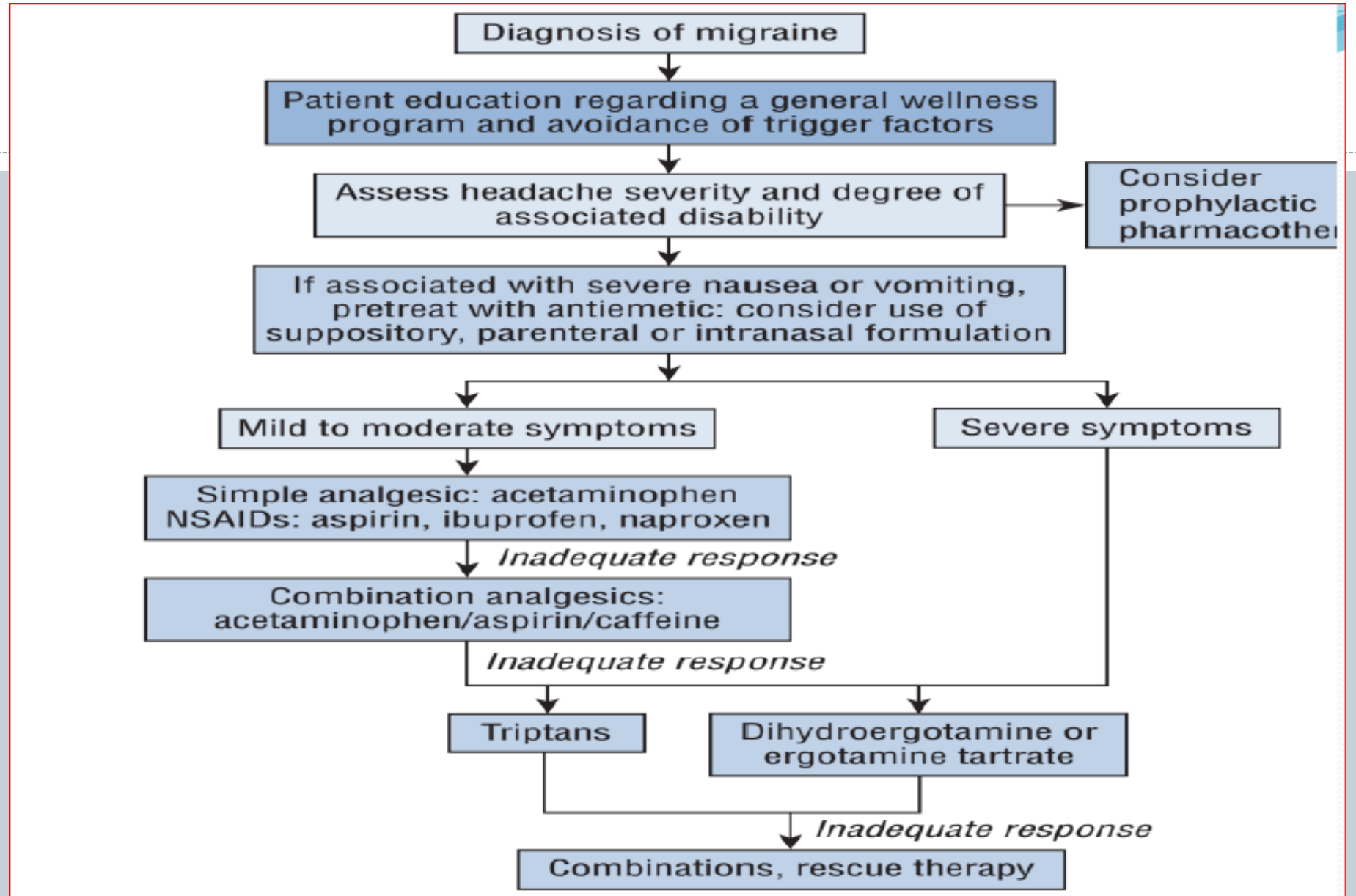
- Antiepileptic Drugs (AEDs)
- ☐ FDA approved for migraine prevention
- ☐ Divalporex Sodium (Depakote)
- ☐ Topiramate (Topamax)

Medications for Prophylaxis of Migraines

Medication (Brand Name)	Usual Dosage (mg/day)	Main Adverse Effects
Antiepileptics:		
Topiramate (Topamax)[a]	50–200	Paresthesias, dizziness, fatigue, nausea
Valproic acid (Depakene)[a]	500–1500	
Divalproex sodium (Depakote)[a]	500–1500	
β-Blockers:		
Atenolol (Tenormin)[b]	50–200	
Metoprolol (Lopressor)[a]	50–200	Fatigue, exercise intolerance
Nadolol (Corgard)[b]	20–160	
Propranolol (Inderal)[a]	80–240	
Timolol (Blocadren)[a]	20–30	
Antidepressants:		
Amitriptyline (Elavil)[a]	10–150	Weight gain, dry mouth, sedation
Venlafaxine (Effexor)[a]	37.5–150	

[a]Level A: Established efficacy.

[b]Level B: Probably effective.



GURE 54–1. Treatment algorithm for migraine headaches.

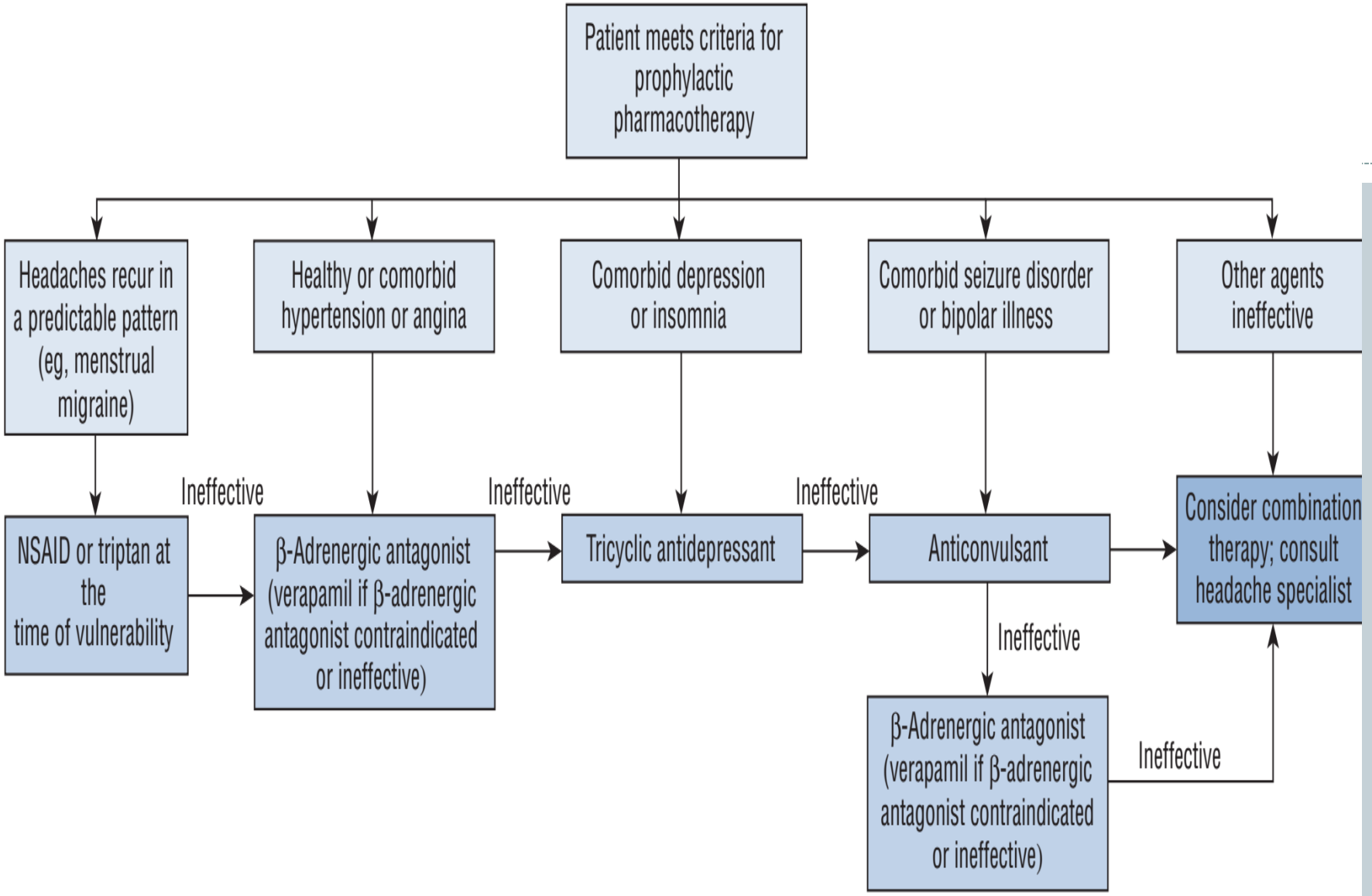


FIGURE 54–2. Treatment algorithm for prophylactic management of migraine headaches. (NSAID, nonsteroidal anti-inflammatory drug.)

TENSION-TYPE HEADACHE (TTH)

- Tension-type headache, the most common type of primary headache, is more common in women than men.
- Pain is usually mild to moderate and nonpulsatile.
- The pain is described by sufferers as a band-like tightness or pressure around the head.
- TTHs occurring more than 15 days per month for more than 3 months, without evidence medication overuse, would be classified as chronic TTH.

- The pathophysiology of TTH is incompletely understood. It seems likely that TTH is due to a primary disorder of central nervous system pain modulation alone, unlike migraine, which involves a more generalized disturbance of sensory modulation.

- useful clinical approach is to diagnose TTH in patients whose headaches are completely without accompanying features such as nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, and aggravation with movement

Clinical Presentation and Diagnosis of Tension-Type Headache

Patients experiencing TTH may display the following headache symptoms and characteristics:

Two or more of the following present:

1. Bilateral pain
2. Nonpulsating pain
3. Mild or moderate pain intensity

Both of the following:

1. No nausea or vomiting (anorexia possible)
2. Either photophobia or phonophobia (not both)

Duration: 30 minutes to 7 days

Criteria for diagnosis: 10 or more attacks fulfilling above criteria occurring on average less than 1 day per month are necessary

Acute Treatment (Episodic TTH)

- First line: OTC analgesics (APAP, NSAIDs)
- Second line: ASA+APAP+caffeine, butalbital containing products
- High risk of rebound headaches
- Limit acute treatment to 2-3 days per week

Preventive Treatment (Chronic TTH)

- Non-Pharmacologic
  - Proper sleep hygiene
  - Stress management
  - Acupuncture
  - Biofeedback
  - Physical therapy

- Pharmacologic
  - TCAs (best efficacy)
  - SSRIs (better tolerated)

**Consider for patients with >15 headaches per month

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

- Cluster headache is one of a group of disorders referred to as trigeminal autonomic cephalalgias.
- This autonomic nervous system dysfunction is characterized by sympathetic underactivity coupled with parasympathetic activation.
- Similar to migraine, the pain of a cluster headache is believed to be the result of vasoactive neuropeptide release and neurogenic inflammation.

Cluster Headache

- Cluster headache is a relatively rare form of primary headache with a population frequency of approximately 0.1%.
- The pain is deep, usually retro-orbital, often excruciating in intensity, non-fluctuating, and explosive in quality.
- A core feature of cluster headache is periodicity.
  - At least one of the daily attacks of pain recurs at about the same hour each day for the duration of a cluster bout.

- Pain associated with cluster headache differs from migraine and TTH in that it is severe, intermittent, and short in duration.
- Headaches typically occur at night, but attacks may occur multiple times per day.
- The pain is usually unilateral, but, unlike migraine, it is not described as pulsatile.
- patients tend to become excited and restless during attacks, rather than seeking quiet and solitude as in migraine.

Clinical Presentation and Diagnosis of Cluster Headache

Patients experiencing "cluster headache" may display the following headache symptoms and characteristics:

At least one or more of the following symptoms:

1. Lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead or facial sweating/flushing
5. Sensation of fullness in the ear
6. Miosis and/or ptosis

Or a sense of restlessness or agitation

Duration of pain: 15–180 minutes (untreated)

Frequency of attacks: One every other day and/or up to 8 per day for more than half the time the disorder is active (may have long periods when headaches are inactive)

Criteria for diagnosis: Five or more attacks fulfilling the above criteria

Cluster headache classification

- Episodic cluster headache : at least two cluster period lasting 7-365 days and separated by pain free remission period of > 1month.
- Chronic cluster headache ; attack recur over period > 1 year with out remission periods or with remission period of < 1month.

Cluster Headache Abortive Treatment

- Inhalation of 100% oxygen up to 15 L/min
- Sumatriptan 4-6mg subQ or 20 mg nasally
- Zolmitriptan 5-10 mg nasally or PO
- Dihdroergotamine 1 mg nasally up to 3 mg in 24 hours
- Prednisone 40-100 mg burst and taper

Cluster Headache Prevention

- ☐Verapamil 120-360 mg PO daily
- ☐Lithium 300 mg PO BID to TID
- ☐Divalproex 500-1500 mg PO daily to BID
- ☐Topiramate 50-200 mg PO divided BID
- ☐Prednisone 40-100 mg burst and taper
- ☐Melatonin 3 mg PO QPM

TABLE 447-8 PREVENTIVE MANAGEMENT OF CLUSTER HEADACHE

Short-Term Prevention	Long-Term Prevention
Episodic Cluster Headache	**Episodic Cluster Headache and Prolonged Chronic Cluster Headache**
Prednisone 1 mg/kg up to 60 mg qd, tapering over 21 days	Verapamil 160–960 mg/d
Methysergide 3–12 mg/d	Lithium 400–800 mg/d
Verapamil 160–960 mg/d	Methysergide[a] 3–12 mg/d
Greater occipital nerve injection	Topiramate[b] 100–400 mg/d
	Gabapentin[b] 1200–3600 mg/d
	Melatonin[b] 9–12 mg/d

[a]Not available worldwide. [b]Unproven but of potential benefit.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor for frequency, intensity, and duration of headaches and for any change in the headache pattern.
- Encourage patients to keep a headache diary to document frequency, duration, and severity of headaches, headache response, and potential triggers of migraine headaches.

- Monitor patients taking abortive therapy for frequency of use of prescription and nonprescription medications and for side effects.
- Document patterns of abortive medication used to establish the need for prophylactic therapy.
- Monitor prophylactic therapies closely for adverse reactions, abortive therapy needs, adequate dosing, and compliance

EPILEPSY

Learning objectives

- ☐*Define seizure and epilepsy*
- ☐*Describe the etiologies, pathogenesis, classification of seizure*
- ☐*Describe the clinical presentation & diagnostic approaches of a patient with seizure and epilepsy*
- ☐*Outline the management principles of seizure and epilepsy*
- ☐*Discuss the role of pharmacist in the management of epilepsy*

Definition

- **Seizure**: is a paroxysmal event due to abnormal, excessive, hypersynchronous discharge of a population of excitatory neurons in the CNS.
- ☐Can be clinical or subclinical
- ☐***Epilepsy*** : a clinical condition of recurrent (two or more) seizures due to a chronic, underlying process (i.e. unprovoked by an acute systemic or brain insult).

- Epilepsy: a disease of the brain defined by
- (i) At least two unprovoked seizures occurring
- > 24 h apart;
- (ii) one unprovoked seizure and a probability of further seizures similar;
- (iii) diagnosis of an epilepsy syndrome

- **Provoked seizures**
- ☐Seizures induced by somatic disorders originating outside the brain
- ☐E.g. fever, infection, syncope, head trauma, hypoxia, toxins, cardiac arrhythmias
- ☐**Status epilepticus (SE)**
- ☐Continuous convulsion lasting longer than 30 minutes OR occurrence of serial convulsions between which there is no return of consciousness

- **Idiopathic SE**
- ☐Seizure develops in the absence of an underlying CNS lesion/insult
- ☐**Symptomatic SE**
- ☐Seizure occurs as a result of an underlying neurological disorder or a metabolic abnormality

EPIDIMOLOGY

- The prevalence of epilepsy in developing country is higher than developed country (Banerjee, P. N., et al. 2009)
- In Ethiopia (Tekle-Haimanot, R., et al. 1997)
- The prevalence was reported as 5.2 per1000 population.
- The incidence was 64 per100,000 population

Etiology of seizures

- Epileptic
  - Idiopathic (70-80%)
  - Cerebral tumor
  - Neurodegenerative disorders
  - Neurocutaneous syndromes
- Secondary to
  - ✓ Cerebral damage: e.g. congenital infections, HIE, intraventricular hemorrhage
  - ➢ Cerebral dysgenesis/malformation: e.g. hydrocephalus

- ❖ Non-epileptic
- ✓ Febrile convulsions
- ❖ Metabolic
- ✓ Hypoglycemia
- ✓ HypoCa, HypoMg, HyperNa, HypoNa
- ☐ Head trauma
- ☐ Meningitis
- ☐ Encephalitis
- ☐ Poisons/toxins

Aetiology of Status Epilepticus

- Prolonged febrile seizure
- ✓ Most common cause
- Idiopathic status epilepticus
- ☐Non-compliance to anti-convulsants
- ☐Sudden withdrawal of anticonvulsants
- ☐Sleep deprivation
- ☐Intercurrent infection
- Symptomatic status epilepticus
- ☐Anoxic encephalopathy
- ☐Encephalitis, meningitis
- ☐Congenital malformations of the brain
- ☐Electrolyte disturbances, drug/lead intoxication, extreme hyperpyrexia, brain tumor

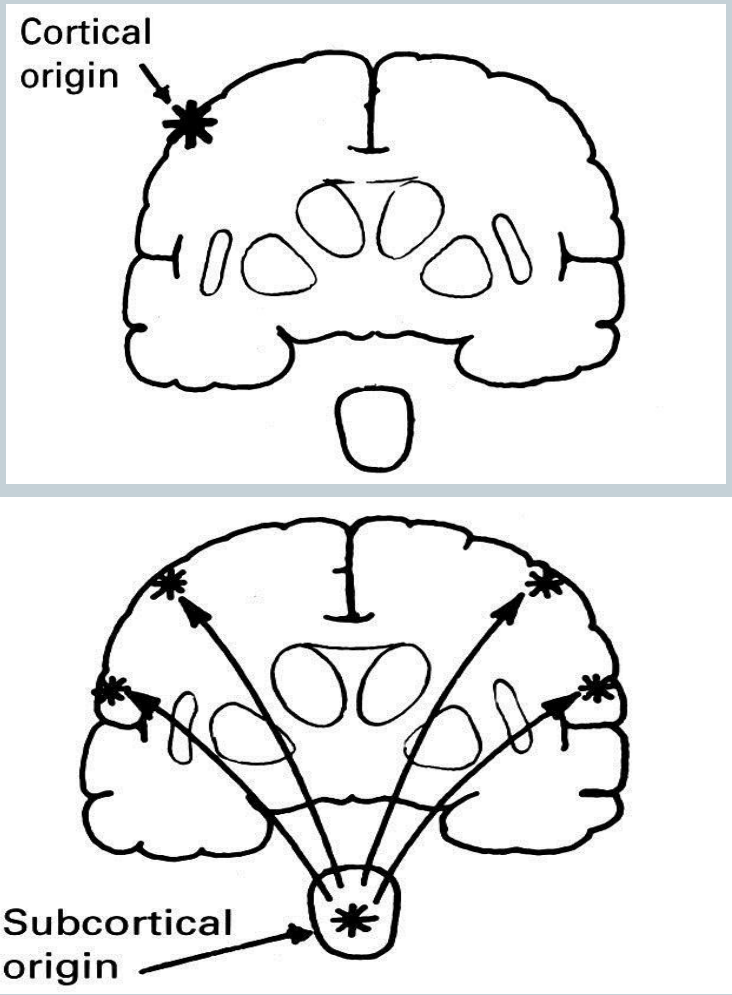
Pathophysiology

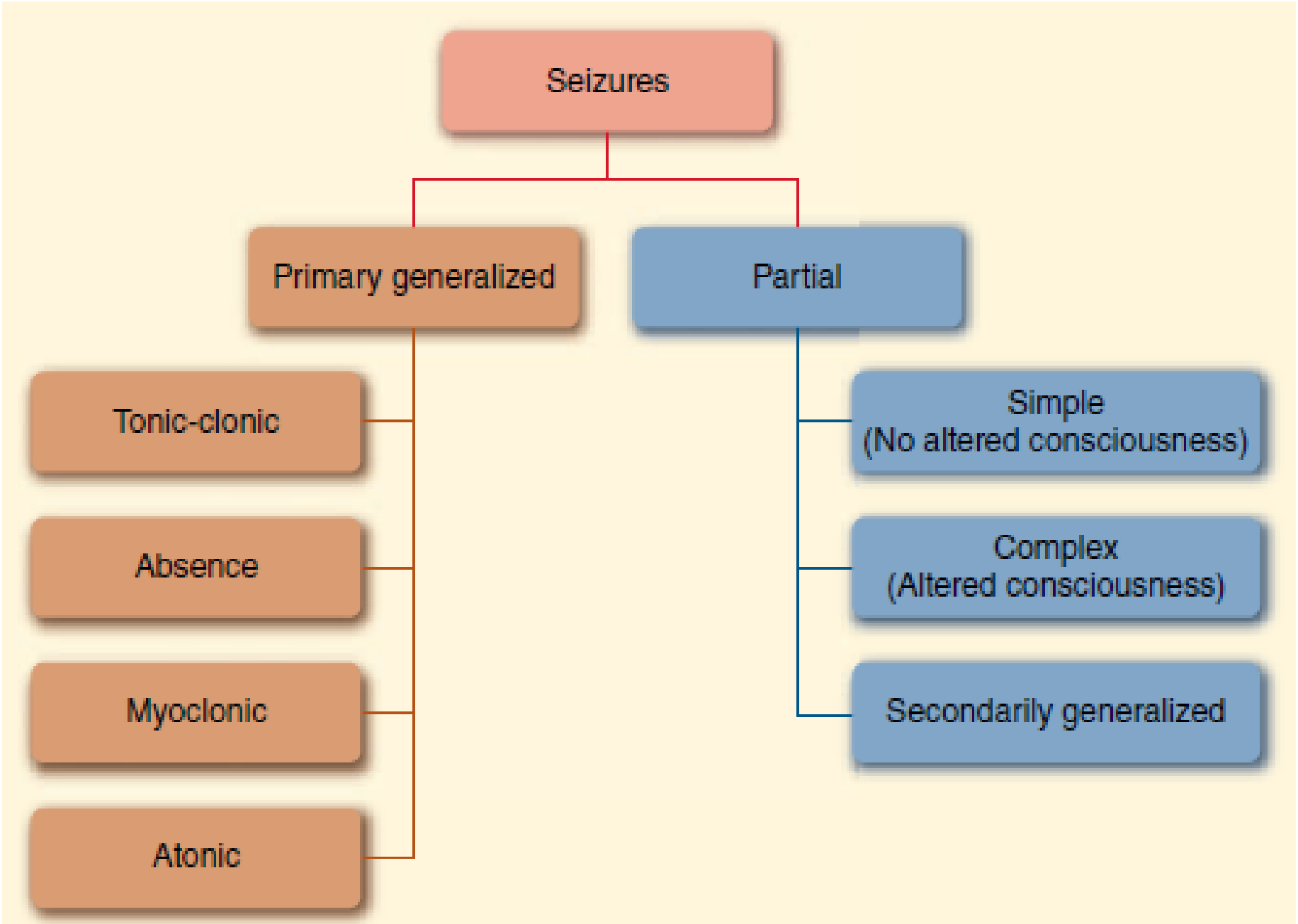
- Still unknown
- Some proposals:
  - Excitatory glutamatergic synapses
  - Excitatory amino acid neurotransmitter (glutamate, aspartate)
  - Abnormal tissues — tumor, AVM, dead area
  - Genetic factors
  - Role of substantia nigra and GABA

- Cortical electrical discharges become excessively rapid, rhythmic, and synchronous.
- This phenomenon is presumably related to an excess of excitatory neurotransmitter action, a failure of inhibitory neurotransmitter action, or a combination of the two.
- In the individual patient, it is usually impossible to identify which neurochemical factors are responsible.

Seizure Types

- Partial Seizures –
  - ✓ *account for 80% of adult epilepsies*
  - ✓ Simple partial
  - ✓ Complex partial
- Generalized Seizures
  - ☐Absence
  - ☐Tonic-clonic
  - ☐Atonic
  - ☐Myoclonic
- Unclassified seizures
  - ☐*Infantile spasms*
- Status epilepticus




Seizures
Primary generalized
Partial
Tonic-clonic
Absence
Myoclonic
Atonic
Simple
(No altered consciousness)
Complex
(Altered consciousness)
Secondarily generalized

- SP seizure
- • Usually last less than one minute
- •no loss of consciousness
- •**Motor symptoms**: abnormal movements of the hand synchronous with movement of the face
- •**Sensory /somatic sensory symptoms**: paresthesias, vision (flashing lights or formed hallucinations), equilibrium (sensation of falling or vertigo), or autonomic function (flushing, sweating, alterations in hearing, olfaction)
- •**Psychic symptoms**: sensation of unusual, intense odors or highly complex sounds, fear, a sense of impending change, detachment, depersonalization, illusions that objects are growing smaller (micropsia) or larger (macropsia).

CP seizures

- •Somatosensory or focal motor & psychiatric features like SP seizure
- •Altered consciousness
- •May begin with an aura
- •Automatisms (lip smacking, chewing, abnormal tongue movements)
- •Generalized seizures
- •May be preceded by an aura
- •Always associated with loss of consciousness.

- Tonic-clonic seizures
- Generally lasts 1 to 3 minutes
- Begin with a short tonic contraction of muscles and a period of rigidity
- Clonic phase of repetitive jerking
- Patient may lose sphincter control, bite the tongue, or become cyanotic
- The episode may be followed by unconsciousness, and frequently the patient goes into a deep sleep.

Absence seizures

- Brief and abrupt (Duration: 10-30 sec) loss of consciousness
- Primarily in children
- Sudden onset
- Usually accompanied by *subtle, bilateral motor signs* (rapid blinking of the eyelids, chewing movements, or small-amplitude, clonic movements of the hands)
- Precipitated by hyperventilation

- Myoclonic jerks
  - Brief shock-like muscular contractions of the face, trunk, and extremities
  - This may be isolated events or rapidly repetitive
- Atonic seizures
  - Sudden loss of muscle tone that may be described as a head drop, dropping of a limb, or slumping to the ground.

Infantile Spasms

- Begin in first 6 months
- Occur in clusters and several times a day
- Described by parents as sounding like colic
- High morbidity and mortality
- Treated with ACTH or oral steroids

Post-traumatic epilepsy

- Seizures that occur after head trauma
- Patients may be started on phenytoin for 7 days. If none occur, then it should be discontinued

- **Treatment**
  - Goals of treatment
    - Decreasing the frequency of seizures to seizure-free state
    - Minimizing side effects
    - Improving functionality & QOL
    - Treating neuropsychiatric comorbidities such as depression, anxiety, and sleep disturbances

- Management principles

☐Treatment of underlying causes

☐Avoidance of precipitating factors

☐Prophylactic therapy with antiepileptic medications or surgery

☐Addressing psychological and social issues

- **Non-drug management**

☐Adequate sleep

☐Avoidance of alcohol, stimulants, etc.

☐Avoidance of known precipitants

☐Stress reduction

☐Avoidance of risky conditions: swimming, firework, machine work, climbing

- **Acute management/First aids**
- Place the patient in semi prone position with head to the side to avoid aspiration
- Support the head to avoid head injury
- Protect from nearby hazards
- Tongue blades or other objects should not be forced between clenched teeth
- Don’t put any object in mouth
- Transfer to hospital needed if
- Multiple seizure or status epilepticus
- Person is pregnant, injured, diabetic
- New onset seizure

Acute mgt (Hospital)

- Oxygen should be given via face mask
- Reversible metabolic disorders should be promptly corrected.
- Give parentral anticonvulsant therapy (diazepam, lorazepam) and consider prophylactic AED therapy.

- **When to Initiate AED**
- Patients who have had *two or more* seizures
- A single seizure due to an identified epileptogenic lesion (CNS tumor, infection, or trauma) and
- Risk factors associated with recurrent seizures
- *An abnormal neurologic examination*
- *Seizures presenting as status epilepticus*
- *A strong family history of seizures*
- *An abnormal EEG*

- Start with *monotherapy* and minimum dose
- Polytherapy:

✓ Maximize the doses & serum concentrations of the first anticonvulsant

✓ Add an anticonvulsant with a different mechanism of action

- **Epilepsy: Drug therapy**

☐Choice of AED based on

☐Seizure type

☐Efficacy

☐Adverse effect

☐Pharmacokinetic profile

☐Cost

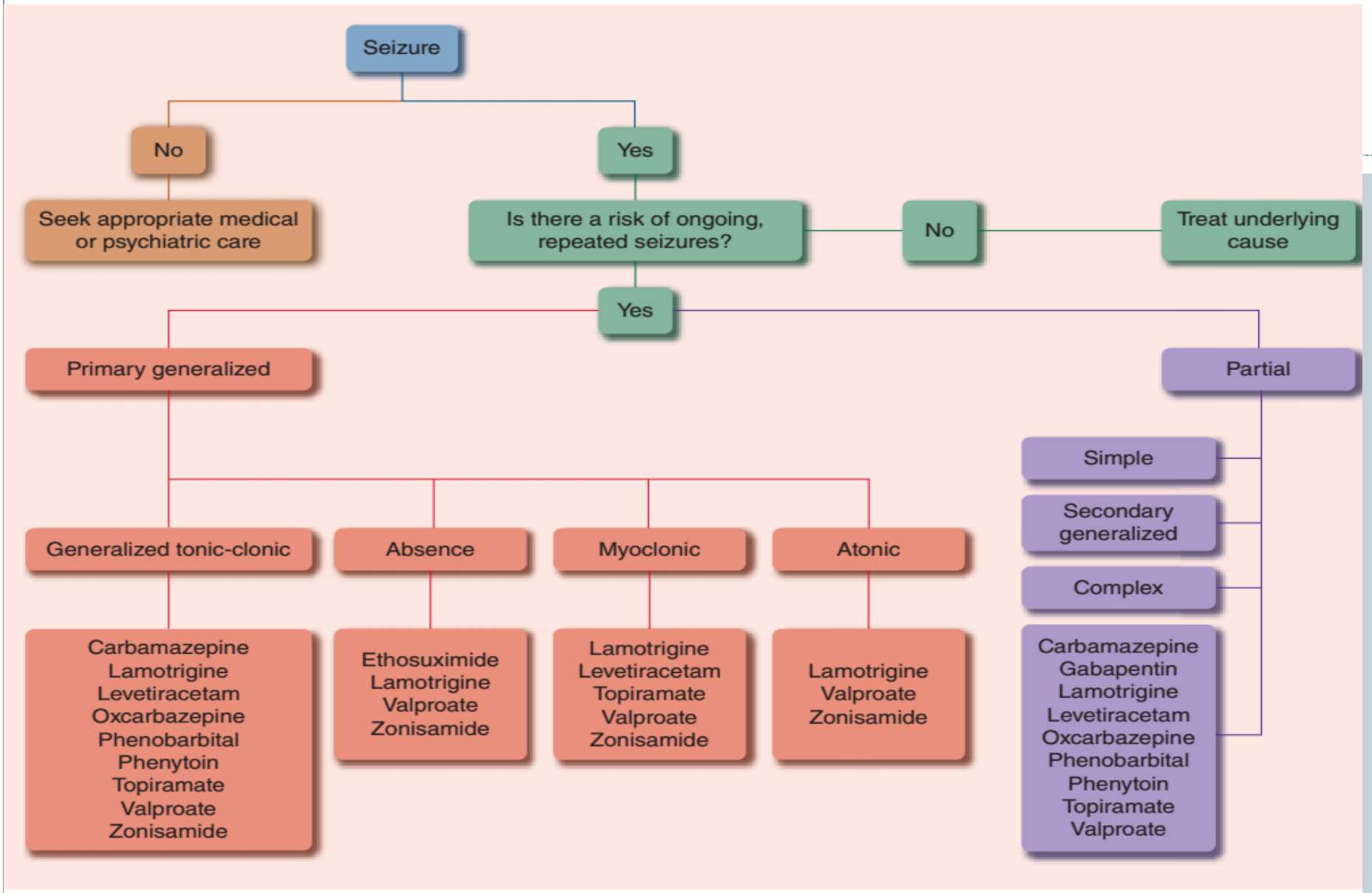
☐Patient preferences

☐Co-morbid conditions

- The traditional treatment of tonic-clonic seizures is **phenytoin** or **phenobarbital**, but **carbamazepine** and **valproic acid** use is increasing, as efficacy is equal and side effects are more favorable.
- **Carbamazepine** and **valproic acid** had equal retention rates for tonic-clonic seizures, but **carbamazepine** was superior for partial seizures and **valproic acid** caused slightly more adverse effects.
- In the United States, **carbamazepine** and **phenytoin** are the most commonly prescribed AEDs for partial seizures.

- **Lamotrigine** is as effective as **carbamazepine** and **phenytoin**; lamotrigine may be better tolerated in the elderly.
- **Levetiracetam** was found to have equal efficacy and tolerability with controlled release carbamazepine.
- The newer AEDs were first approved as adjunctive therapy for refractory partial seizures.
- To date, **lamotrigine**, **topiramate**, **oxcarbazepine**, and **felbamate** have FDA approval as monotherapy in patients with partial seizures

- Absence seizures are best treated with **ethosuximide**, **valproic acid**, and perhaps **lamotrigine**.
- For a combination of absence and other generalized or partial seizures, **valproic acid** or lamotrigine is preferred.
- If valproic acid is ineffective in treating a mixed seizure disorder that includes absence, **ethosuximide** should be used in combination with another AED.



URE 31–2. Treatment algorithm for management of seizure disorders.

- **Phenytoin**, **carbamazepine**, **phenobarbital**, **oxcarbazepine**, **felbamate**, and **valproic acid** may interfere with vitamin D metabolism
- Patients taking these drugs should get supplemental vitamin D and calcium and BMD testing if other risk factors for osteoporosis are present

Principles of Drug Treatment

- Start with an average dose of a first line drug
- Poor control? Address compliance, maximize drug dose, confirm right diagnosis (partial complex v.s generalized)
- Majority of patients are controlled with single antiepileptic drug.
- This drug can be gradually withdrawn if seizure free for two years.
- Seizures recur in 25% of patients without risk factors and 50% of patients with risk factors.
- The drug can be reduced by 25% every two to four weeks.

- 20-35% of patients with epilepsy have persistent seizures despite medical therapy.
- ☐If poor control with maximal dose, monotherapy with second drug.
- ☐Continue to administer first drug until a full dose of second drug reached, then gradually withdraw first drug.
- ☐If monotherapy with two drugs fail, patient may need re-evaluation (repeat MRI/EEG) before polytherapy commenced

When to Switch Therapy

- *If seizures continue* despite gradual increases to the maximum tolerated dose and documented compliance.
- *Intolerable side effects*

✓ Maintaining the patient on the first drug while a second drug is added, then the first drug can be gradually withdrawn (usually over weeks unless there is significant toxicity). The dose of the second drug is then further optimized based on seizure response and side effects

↑GABA

Barbiturates
Benzodiazepines
Gabapentin
Levetiracetam
Tiagabine
Topiramate
Valproate
Vigabatrin

↓Na^+

Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Topiramate
Valproate

↓Ca^{2+}

Ethosuximide
Levetiracetam
Pregabalin
Valproate

❖ When to Discontinue Therapy

- Therapy can be withdrawn in patients of :

✓ Complete medical control of seizures for >2 years

✓ Single seizure type, either partial or generalized

✓ Normal neurologic examination, including intelligence

✓ Normal EEG

- ☐It should be performed very carefully and slowly! Reduce the dose of the drug gradually over 2–3 months
- ☐20% of pts will suffer a further sz within 2 yrs.

- **Special Populations**
- Children and women with epilepsy have unique problems related to the use of AEDs.
- In children, developmental changes occur rapidly, and metabolic rates are greater than those seen in adults.
- When treating a child, it is imperative to control seizures as quickly as possible to avoid interference with development of the brain and cognition

- AED doses are increased rapidly, and frequent changes in the regimen are made to maximize seizure control.
- Due to rapid metabolic rates seen in children, doses of AEDs are typically higher on a milligram per kilogram basis compared with adults,
- and serum concentrations are used more extensively to help ensure an adequate trial of a drug has been given.

- For women,

✓ the treatment of epilepsy poses challenges, including teratogenicity, breastfeeding, interactions between AEDs and hormonal contraceptives, and reduced fertility.

✓ Recommendations are developed for managing women of childbearing potential and who are pregnant

- The risk of teratogenicity is well known (~5%), especially with valproates, but withdrawing drug therapy in pregnancy is more risky than continuation.
- Epileptic females must be aware of this problem and thorough family planning should be recommended. Over 90% of pregnant women with epilepsy will deliver a normal child.

- Neural tube defects (eg, spina bifida, microcephaly, anencephaly) are associated most commonly with valproate and possibly carbamazepine.
- Additionally, valproate is associated with impaired cognitive development in children born to women taking valproate during pregnancy.
- It is best to avoid the use of valproate, if possible, in women of childbearing potential

- All women of childbearing potential who take AEDs should take 1 to 4 mg daily of supplemental **folic acid** to reduce the risk of birth defects.
- Higher folate doses should be used in women with a history of a previous pregnancy with a neural tube defect or taking valproic acid.
- **Vitamin K**, 10 mg/day orally, given to the mother during the last month before delivery can prevent neonatal hemorrhagic disorder. Alternatively, parenteral vitamin K can be given to the newborn at delivery.

- **Status Epilepticus**
- ☐is any seizure lasting longer than 30 minutes whether or not consciousness is impaired, or
- ☐recurrent seizures without an intervening period of consciousness between seizures.
- ☐Medical emergency with significant morbidity and mortality
- ☐Classified as GCSE and NCSE

Status Epilepticus

- ☐is any seizure lasting longer than 30 minutes whether or not consciousness is impaired, or
- ☐recurrent seizures without an intervening period of consciousness between seizures.
- ☐Medical emergency with significant morbidity and mortality
- ☐Classified as GCSE and NCSE

Morbidity and mortality

- Younger children, the elderly, and those with preexisting epilepsy have a higher propensity for sequelae.
- A mortality rate of up to 10% in children, 20% in adults, and 38% in the elderly.
- Variables affecting outcome are

- (1) the time between onset of GCSE and the initiation of treatment, and
- (2) the duration of the seizure.

Clinical presentation and diagnosis

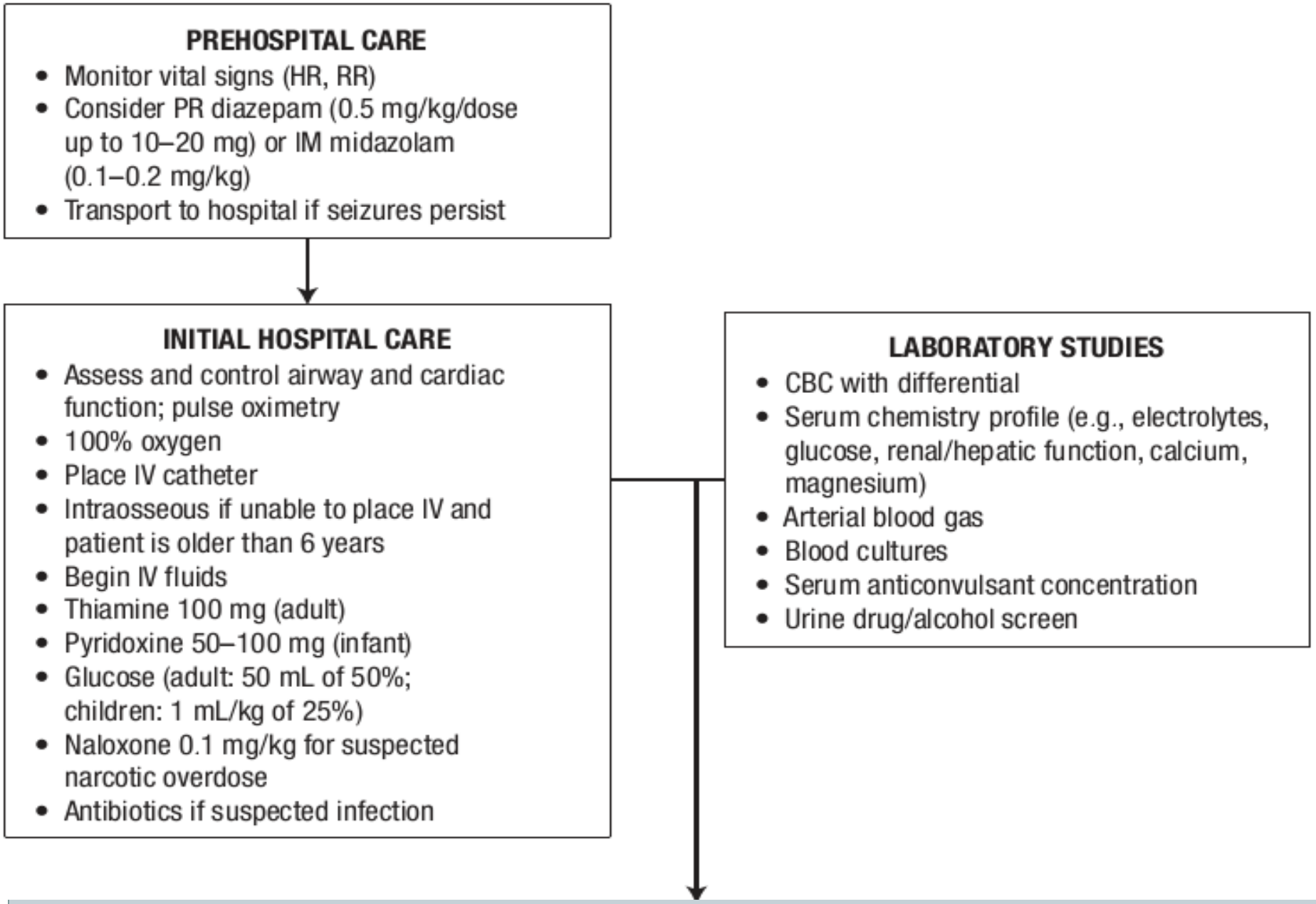
- SYMPTOMS
- Impaired consciousness
- Disorientation (once GCSE is controlled)
- Pain associated with injuries

- Early SIGNS Generalized convulsions

☐ Acute injuries
☐ Hypothermia or fever
☐ Incontinence
☐ Normal BP or hypotension
☐Respiratory compromise

- Late Signs

☐ Clinical seizures may or may not be apparent
☐ Pulmonary edema with respiratory failure
☐ Cardiac failure (dysrhythmias, arrest, cardiogenic shock)
☐ Hypotension/hypertension
☐ Disseminated intravascular coagulation, multiorgan failure
☐ Rhabdomyolysis
☐ Hyperpyremia


PREHOSPITAL CARE
• Monitor vital signs (HR, RR)
• Consider PR diazepam (0.5 mg/kg/dose up to 10–20 mg) or IM midazolam (0.1–0.2 mg/kg)
• Transport to hospital if seizures persist
INITIAL HOSPITAL CARE
• Assess and control airway and cardiac function; pulse oximetry
• 100% oxygen
• Place IV catheter
• Intraosseous if unable to place IV and patient is older than 6 years
• Begin IV fluids
• Thiamine 100 mg (adult)
• Pyridoxine 50–100 mg (infant)
• Glucose (adult: 50 mL of 50%; children: 1 mL/kg of 25%)
• Naloxone 0.1 mg/kg for suspected narcotic overdose
• Antibiotics if suspected infection
LABORATORY STUDIES
• CBC with differential
• Serum chemistry profile (e.g., electrolytes, glucose, renal/hepatic function, calcium, magnesium)
• Arterial blood gas
• Blood cultures
• Serum anticonvulsant concentration
• Urine drug/alcohol screen

EARLY STATUS

0–10 minutes

- IV Lorazepam (4 mg adults; 0.03–0.1 mg/kg at 2 mg/min pediatrics) may repeat if no response in 5 minutes
- Additional therapy may not be required if seizures stop and cause identified

10–30 minutes

- IV Phenytoin or fosphenytoin PE[a] adults: 10 to 20 mg/kg at rate of 50 mg/min or 150 mg/min PE, respectively; infants/children: 15 to 20 mg/kg at a rate of 1 to 3 mg/kg/min

STAGE OF ESTABLISHED STATUS (30–60 minutes)

Seizures continue:

- Additional IV 5 mg/kg dose of either phenytoin or fosphenytoin PE[a] may be given to unresponsive patients[b]
- IV Phenobarbital[a] 20 mg/kg at a rate of 100 mg/min in adults and 30 mg/min in infants/children[b]

STAGE OF REFRACTORY STATUS (greater than 60 minutes)

Clinical or electrical seizures continue:

- IV Phenobarbital[a] additional 10 mg/kg; 10 mg/kg may be given every hour until seizures stop *or*
- IV Valproate 15–25 mg/kg followed by 1 to 4 mg/kg/hour[b] *or*
- General anesthesia with either
  IV Midazolam 2 mg/kg bolus followed by 50 to 500 mcg/kg/hour
  IV Pentobarbital 15 to 20 mg/kg bolus over 1 hour then 1 to 3 mg/kg/hour to burst suppression on EEG. If hypotension occurs slow rate of infusion or begin dopamine or
  IV Propofol 1 to 2 mg/kg bolus followed by ≤4 mg/kg/hour

Once seizures controlled, taper midazolam, pentobarbital, propofol over 12 hours. If seizures recur restart infusion and titrate to effective dose over 12 hours

Carbamazepine

- ☐Food may enhance the bioavailability of **carbamazepine**.
- Leukopenia is the most common hematologic side effect (up to 10%) but is usually transient. It may be persistent in 2% of patients

- **Ethosuximide**

☐No loading dose is needed; titration over 1 to 2 weeks to maintenance doses of 20 mg/kg/day usually produces therapeutic serum concentrations.

☐It is usually given in two equal doses daily.

☐Valproic acid may inhibit metabolism of **ethosuximide**, but only if the metabolism of ethosuximide is near saturation

Phenobarbital

- a potent enzyme inducer, interacts with many drugs. Diuretics and urinary alkalinizers increase the amount of phenobarbital excreted renally

- **Ethanol** increases phenobarbital metabolism, but **valproic acid**, **cimetidine**, and **chloramphenicol** inhibit its metabolism.
- Phenobarbital can usually be dosed once daily, and bedtime dosing may minimize daytime sedation

Phenytoin

- is a first-line AED for primary generalized convulsive seizures and for partial seizures.
- Food may slow absorption. The intramuscular route is best avoided, as absorption is erratic.
- Fosphenytoin can safely be administered IV and intramuscularly, and it is ordered in phenytoin equivalents

Valproic acid

- It is first-line therapy for primary generalized seizures, such as absence, myoclonic, and atonic seizures, and is approved for adjunctive and monotherapy treatment of partial seizures. It can also be useful in mixed seizure disorders.
- GI complaints may be minimized with the enteric-coated formulation or by giving with food.
- is common but is responsive to a decrease in dose.

- **Lamotrigine**

It is useful as both adjunctive therapy for partial seizures and as monotherapy.

- It may also be a useful alternative for primary generalized seizures, such as absence and as adjunctive therapy for primary GTC seizures.

- Rashes are usually generalized, erythematous, and morbilliform, but Stevens– Johnson reaction has also occurred.

Thank you