Antimigraine drugs

What is migraine?
- Repeated attacks of headache
- Often only one side of the head hurts
- Preceded by visual or other aura
- Light and sound hypersensitivity
- Often experience loss of appetite, nausea and vomiting

Migraine facts
- Migraine is one of the common causes of recurrent headaches (16% of primary headaches)
- Migraine affects 10-20% of general population
- Migraine often is undiagnosed and untreated
- Migraine greatly affects the quality of life
- In childhood migraine, boys and girls are affected equally, until puberty, when the predominance shifts to girls (adults – female:male ratio is 2:1)

Migraine triggers
- Food
- Disturbed sleep pattern
- Hormonal changes
- Drugs
- Physical exertion
- Visual stimuli
- Auditory stimuli
- Olfactory stimuli
- Weather changes
- Hunger
- Psychological factors

Types of migraine
Migraine without aura (common migraine)
- Headache lasting 4–72 h (2–48 h in children)
- With at least two of:
  - unilateral location
  - pulsating quality
  - moderate/severe intensity
  - aggravated by activity
- Accompanied by at least one of:
  - nausea
  - vomiting
  - photophobia and/or phonophobia
- No evidence of organic disease

Migraine with aura (classic migraine)
- Headache shortly follows or accompanies aura
- Accompanied by at least one of:
  - nausea
  - vomiting
  - photophobia and/or phonophobia
- No evidence of organic disease

Phases of acute migraine
- Prodrome – vague premonitory symptoms that begin from 12 to 36 hours before headache (yawning, excitement, depression, craving or distaste of various foods)
- Aura – warning or signal before onset of headache
- Headache
- Postdrome – following headache (fatigue, depression, exhaustion)
Aura

- Aura is a warning or signal before onset of headache
- Symptoms
  - Flashing of lights
  - Zig-zag lines
  - Difficulty in focusing
- Duration: 15-30 min

Headache

- Generally unilateral and associated with symptoms like:
  - Anorexia
  - Nausea
  - Vomiting
  - Photophobia
  - Phonophobia
  - Tinnitus
- Duration: 14 – 72 hrs

Migraine - pathophysiology

**PRESENT UNDERSTANDING**

- Neurovascular process, in which neural events result in activation of blood vessels, which in turn results in pain and further nerve activation

**VASCULAR THEORY**

- Aura – intracerebral blood vessel vasoconstriction
- Headache – intracranial/Extracranial blood vessel vasodilation

**SEROTONIN THEORY**

- Decreased serotonin levels linked to migraine
- Plasma and platelet concentration of serotonin vary with the different phases of migraine attack
- Specific serotonin receptors found in blood vessels of brain
- Migraine may be precipitated by agents such as reserpine that release biogenic amines, including serotonin from intracellular storage sites

Migraine treatment

- Abortive – to prevent a migraine attack or to stop it once it starts
- Preventive – to lessen the frequency and severity of the migraine attacks

Medicines to stop a migraine attack

- Triptans, dihydroergotamine
- NSAIDs (ibuprofen, naproxen)
- Aspirin, acetaminophen – combinations with caffeine

Triptans (sumatriptan)

- Mimics the action of serotonin by binding to serotonin 5-HT1 receptors and causing blood vessels to constrict
- Available in oral, nasal, and injection form
- Rapidly absorbed after oral or subcutaneous administration, relief of symptoms occurs 10 to 90 minutes after SC administration, and 1.5 to 2 hours after oral and nasal administration.
- Side effects – nausea, dizziness, and muscle weakness
- Newer drugs – rizatriptan, naratriptan, zolmitriptan, almotriptan, frovatriptan and eletriptan
  - Provide pain relief within two hours for most people
  - Fewer side effects
  - Fewer recurring headaches
Ergot derivatives

- Ergot – product of fungus Claviceps purpurea
- Natural alkaloid – ergotamine; semisynthetic derivative – dihydroergotamine
- Nonselective pharmacological agents
- Used for acute relief of migraine; the use should be restricted to patients having frequent moderate migraine attacks or infrequent but severe attacks
- Adverse effects – nausea, vomiting, leg weakness, muscle pain
- Contraindications – pregnancy!!!
Intermittent claudication
- Ischemia of the leg muscles due to sclerosis and narrowing of arteries
- Attacks of lameness and pain brought on during walking
- Other cardiovascular diseases
  - 10% – cerebral stroke
  - 28% – coronary artery disease

Chronic ischemia
- Narrowing of the arteries of the extremities due to atherosclerosis
- Common complication of arteriosclerosis in which the vascular system of the legs become blocked

Chronic ischemia - treatment
- Patient teaching
  - Walking
  - Not sitting or standing in one position for long periods
  - Not crossing legs
- Pharmacological therapy
- Surgical treatment

Acute ischemia
- Arterial thrombi
- Stasis thrombi dislocation
- Treatment – surgical
- Treatment of pain: slow-release opiate
- Prostacyclin analogues (Iloprost, Alprostadil)
- Chemical or surgical lumbar sympathectomy
- Dorsal column spinal stimulation
- Prophylaxis – heparin, oral anticoagulants

Vasculitis
- Inflammation of vessels and surrounding area caused by immune complex deposition
- Vessels → necrosis, infiltration of lymphocytes and eosinophils → ischemia of related tissue
  - Systemic necrotizing vasculitis
  - Hypersensitivity vasculitis
  - Cardiac transplant rejection

Takayasu syndrome
- Vasculitis involving the aortic arch as well as other major arteries → HF, cerebrovascular incidences
- Glucocorticosteroids
Raynaud disease
- Bouts of intense arteriolar vasoconstriction in arteries of fingers and toes
- Condition precipitated by cold or vibration
  - Alpha-1 adrenoreceptor antagonists
  - Direct-acting vasodilators (nitrates)
  - Calcium channel antagonists
  - ACE inhibitors
  - Prostacyclin

Thromboangiitis Obliterans (Buerger’s Disease)
- Inflammation or vasculitis of small and medium sized arteries and veins in the extremities
- Thrombus formation occurs and occludes vessels
- Cause is unknown

Thromboangiitis Obliterans (Buerger’s Disease)
- Clinical manifestations
  - Claudication with exercise in arches of feet
  - Digital pain which may be constant
  - Intense rubor or cyanosis of feet when dependent
  - Absent or decreased pedal or radial pulses
  - Ulcerations and gangrene commonly occur

Groups of medicaments
- Alpha-adrenolytic drugs
- Beta-adrenergic drugs
- Smooth muscle relaxants
- Drugs with reologic properties
- Anti-serotonin drugs
- 5-HT receptor activating drugs

Alfa-adrenolytic drugs - Nicergolin
- Potent vasodilator (improves brain blood flow).
- On the cerebral level it prompts:
  - A lowering of vascular resistance
  - An increase in arterial flow
  - Stimulates the use of oxygen and glucose
  - Stimulates the metabolism of ischemic tissues
  - Improves blood circulation in the lungs and limbs

Alfa-adrenolytic drugs – Nicergolin
MODE OF ACTION
- Nicergolin acts by inhibiting the postsynaptic alpha(1)-adrenoceptors on vascular smooth muscle → ↓ the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine) → peripheral vasodilation
- An increase of vascular circulation in the brain → the enhance of the transmission of nerve signals across the nerve fibres, which secrete acetylcholine as a neural transmitter (nootropic action)
- Inhibition of blood platelet aggregation
Alfa-adrenolytic drugs – Nicergolin

**INDICATIONS**
- senile dementia
- transient ischemia
- chronic ischemic disorders (after stroke, cranial trauma, thrombus/embolus)
- migraines of vascular origin
- platelet hyper-aggregability
- macular degeneration

**CONTRAINDICATIONS**
- Cardiac shock
- Hypotension
- Acute myocardial infarction
- Acute bleeding
- Pregnancy and breast feeding

**SIDE EFFECTS**
- Drowsiness
- Dizziness
- Nausea
- Hypotension (including orthostatic hypotension)
- Gastrointestinal disturbances
- Sleep disorders

Alfa-adrenolytic drugs – Moxisylyte (thymoxamine)

**INDICATIONS**
- Raynaud’s disease
- Frost-bites
- Stroke
- Meniere’s disease

**CONTRAINDICATIONS**
- Pregnancy
- Allergy
- Diabetics and elderly people – with caution

**Side effects:**
- GI disturbances
- Headaches
- Dizziness
Alfa-adrenolytic drugs – Buflomedil

- Alfa-adrenergic receptor blocker in vascular smooth muscle cells
- Weak and non-specific blocker of calcium channels
- Phosphodiesterase inhibitor
- Inhibitor of platelet aggregation

INDICATIONS
- Intermittent claudication
- Ulceration of lower limbs (other therapy unsuccessful)
- Raynaud’s disease

CONTRAINDICATIONS
- Hypersensitivity
- Arterial bleeding
- Acute MI
- Untreated or unstable CHF
- Pregnancy/breast feeding (cat. C)
- Low DBP (<90mmHg)
- Epilepsy

ADVERSE EFFECTS
- GI disturbances
- Headache
- Tachycardia, reflex hypotonia
- Pseudo-epileptic attacks

Beta-adrenergic drugs - Bamethan

- Epinephrine derivative
- Activates beta2-adrenergic receptors → vasodilation
- Increases the heart contraction → improves the tissue perfusion

INDICATIONS
- Intermittent claudication
- Raynaud’s phenomenon
- Bed sores
- Postthrombotic syndrome

ADVERSE EFFECTS:
- Palpitations
- Dizziness
- Hypotonia

CONTRAINDICATIONS
- Angina pectoris
- Acute MI
- Tachycardia
- Stomach ulcers
- Hyperthyroidism
Beta-adrenergic drugs – Isoxsuprine

- Activates beta2-adrenergic receptors → vasodilation (esp. in muscles)
- Increases tissue histamine release
- Increases heart rate

**INDICATIONS**
- Cerebral vascular insufficiency
- Arteriosclerosis obliterans
- Buerger disease
- Raynaud disease

**CONTRAINDICATIONS**
- Allergy
- Arterial bleeding
- Pregnancy/labour (cat. C)

**SIDE EFFECTS**
- Dizziness, flushing, stomach upset, loss of appetite, nausea, trembling, weakness or nervousness aggravated by alcohol consumption

Beta-adrenergic drugs – Bufenine

- Activates beta-adrenergic receptors → vasodilation (arterioles)
- Positive inotropic activity
- Indicated in peripheral vascular disorders involving arteriolar contraction and premature labour treatment
- Contraindicated in IHD, arrhythmias, hyperthyroidism

Smooth muscle relaxants (spasmolytic drugs, peripheral vasodilators)

- Nicotinic acid derivatives – nicametate
- Calcium channel blockers – cinnarizine
- Vasodilators - bencyclane, vinpocetine, cyclandelate, alprostadil, cilostazol
- Rheological agents – pentoxyphiline

Nicotinic acid derivatives – nicametate

- Converted to nicotinic acid
- Releases the tension of vascular smooth muscle
- Causes vasodilation
  - Improves perfusion (also in the CNS)
  - Reduces the tissue oxygen demand
  - Improves the tissue nutrition
  - Slightly reduces elevated blood pressure
  - High doses: reduction of cholesterol level
Nicotinic acid derivatives – nicametate

**INDICATIONS**
- Cerebrovascular disturbances
- Post-ischemic conditions
- Raynaud disease
- Buerger disease
- Leg ulcers
- Bed sores
- Vascular problems due to diabetes

**CONTRAINDICATIONS**
- Glaucoma
- Liver diseases
- Kidney failure
- Hypersensitivity
- Acute MI
- Acute haemorrhage
- CHF
- Pregnancy

Nicotinic acid derivatives – nicametate

**SIDE EFFECTS**
- Facial flushing
- Dry skin
- GI disturbances
- Skin allergy
- Dizziness and headaches
- Transient hypotonia

Calcium channel blockers – cinnarizine

**INDICATIONS**
- Adjunct therapy for symptoms of peripheral arterial disease
- Control of vestibular symptoms of both peripheral and central origin and of labyrinthine disorders including vertigo, dizziness, tinnitus, nystagmus, nausea and vomiting.
- Prophylaxis of motion sickness.

**ADVERSE EFFECTS**
- Antihistaminic
- Central effects
- GI disturbances
- Antimuscarinic effect

**CONTRAINDICATIONS**
- Pregnancy/breast feeding
- Hypersensitivity
- Parkinson’s disease
**Vasodilators - Bencyclane**

- Relaxation of vascular smooth muscles
- Vasodilation
- Local anaesthetic action
- Reduction of platelets aggregation

**INDICATIONS**
- Cerebrovascular disturbances
- Intermittent claudication
- Raynaud disease
- Microangiopathies
- Arterial constriction after surgical procedures

**CONTRAINDICATIONS**
- Kidney failure
- Liver diseases
- Breathing difficulties
- Cardiac and pulmonary disorders
- PBH

**SIDE EFFECTS**
- Hallucinations, dizziness, headaches, sleep disturbances, dry mouth, nausea, diarrhoea, leucopenia

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**Vasodilators – Vinpocetine**

**INDICATIONS** – Cerebral disturbances caused by
- Ischemic stroke
- Vascular stupor
- Cerebral arteriosclerosis
- Encephalopathy (hypertensive, traumatic)
- Neurological and psychological disorders

**CONTRAINDICATIONS**
- Hypersensitivity
- Pregnancy/breast feeding
- Children

**SIDE EFFECTS**
- Sleep disorders, dizziness, headache, changes in ECG (ST segment, QT interval), GI disturbances; enhances the hypotensive effect of methyl-DOPA

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**Vasodiators – Cyclandelate**

- Causes vasodilation, especially arteries
- Improves blood flow

**INDICATIONS**
- Intermittent claudication
- Arteriosclerosis
- Raynaud’s disease
- Nighttime leg cramps
- Mental/memory disorders
- Prevention of migraine attacks
- Dizziness
- Diabetic nerve pain/tingling

**CONTRAINDICATIONS**
- Blood disorders
- Cerebrovascular disorders
- Glaucoma
- Allergies
- Pregnancy/breast

**ADVERSE EFFECTS**
- Heartburn
- Stomach upset
- Flushing
- Headache
- Weakness
- Tachycardia
- Chest pain
- A pounding heartbeat
- Skin rash

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**Vasodiators – Alprostadil**

- Synthetic prostaglandin PGE1
- Endogenous PGE1:
  - Is produced by endothelium
  - Protects endothelium from damage
  - Causes the dilation of arterioles
  - Reduces the activity of platelets and decreases their aggregation
  - Displays the rheological activity
  - Reduces the myocytes proliferation
  - Inhibits the neutrophile activity
  - Activates the contractions of uterus and stomach

**INDICATIONS**
- Erectile problems
- Chronic arteriolar ischemia leading to stenosis of the arteries
- Treatment of pulmonary artery stenosis, coarctation of the aorta and Fallot’s tetralogy (until surgical treatment)

**CONTRAINDICATIONS**
- Pregnancy/factication
- Unstable CHF
- Atrial fibrillation
- MI/HD
- Liver failure
- Stomach ulcer
- Pulmonary edema
- Severe COPD

**SIDE EFFECTS:**
- Headache, GI disturbances, skin flushing, paresthesia, palpitations, episods of hypotonia
Vasodilators – cilostazol

- Phosphodiesterase inhibitor ⇒ ↑cAMP in the smooth muscle and platelets
- Causes vasodilation
- Inhibits platelet aggregation

INDICATIONS
- Intermittent claudication (preferred in patients with lifestyle-limiting claudication)

Improves pain-free and maximal walking distance
- Patients may experience a benefit at weeks two and four
- Treatment for at least 12 weeks is preferred for maximal benefit

Rheological agents – Pentoxyphylline

- A methylxanthine derivative that inhibits phosphodiesterase and affects blood rheology
- Improves blood flow by increasing erythrocyte and leukocyte flexibility
- Inhibits platelet aggregation
- Reduces viscosity ⇒ improves blood flow
- Pentoxyphylline modulates immunologic activity by stimulating cytokine production

INDICATIONS
- Peripheral vascular diseases
- The management of cerebrovascular insufficiency
- Sickle cell disease
- Diabetic neuropathy

CONTRAINDICATIONS
- GI disturbances: dyspepsia, nausea
- Cardiovascular disorders
- Allergy

SIDE EFFECTS
- GI disturbances: dyspepsia, nausea
- Cardiovascular disorders
- Allergy
<table>
<thead>
<tr>
<th>Venous disease</th>
<th>Sodium tetradecyl sulfate</th>
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<tbody>
<tr>
<td>- Varicose veins</td>
<td>- Injected to veins as sclerotherapy</td>
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<tr>
<td>- Venous thrombosis</td>
<td>- Causes the inflammation of the intima and thrombus formation, which usually occludes the vein</td>
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<tr>
<td></td>
<td>- The subsequent formation of fibrous tissue results in complete occlusion and subsequent loss of the vein</td>
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<tr>
<th>Venous thrombosis</th>
<th>Superficial thrombophlebitis</th>
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<tr>
<td>- Consists of coagulated blood with the small component of platelet aggregation</td>
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<tr>
<td>- Superficial thrombophlebitis</td>
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<tr>
<td>- Deep vein thrombosis</td>
<td>- NSAIDs</td>
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<tr>
<td></td>
<td>- Hyaluronidase (improves circulation)</td>
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<tbody>
<tr>
<td>- Large doses of heparin</td>
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<tr>
<td>- Oral anticoagulants</td>
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<tr>
<td>- Streptokinase</td>
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