MIGRAINE OUTCOME : LATEST APPROACH IN PREVENTION THERAPIES

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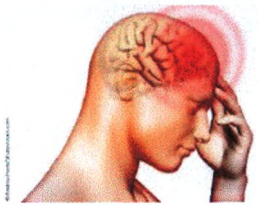
DEFINITION

- Migraine is a cyclic disorder and chronic neurologic disease characterized by attacks of throbbing, often unilateral headache that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting.



American Headache Society. The American Headache Society Position Statement On Integrating New Migrain Treatment Into Clinical Practice.*Headache*.2019;59:1-18

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ORGANISASI : IDI Cab. Padang Perdossi Cab. Padang

MIGRAINE PROBLEMS

Migraine is Common

- Global: 1,04 billion people, South East Asia : 84,39 million people, and Indonesia : 33,1 million people
- 18·9% women and 9·8% men, prevalence peaked in middle life

Migraine is Disabling

- Migraine caused 45·1 million YLDs (years of life lived with disability) globally in 2016.
- Of all migraineurs, 31.3% had an attack frequency of three or more/month, and 53.7% reported severe impairment or the need for bed rest.

Migraine is Costly

- In USA, direct costs $2.7 billion spent for prescription drugs and $730 million for hospital care.

- Global Burden of Disease 2016 Headache Collaborator Group. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; 17: 954–76.

MIGRAINE PROBLEMS

Migraine is underdiagnosed

- World-wide, 60% of individuals with migraine are not professionally diagnosed
- Less than 50% of patients consult a clinician
- There is a lack of professional training:

Migraine is undertreated

- World-wide, about 50% of people with migraine are self-medicating
- In the AMPP study of migraine treatment:
  - 49% used OTC medication only
  - 29% used prescription and OTC medication
  - Only 1 in 8 received preventive therapy

Migraine disability can be asses by MIDAS (Migraine Disability Assessment) and MSQ (Migraine specific Questionnaire

- Diamond S et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache 2007;47:355.

THE AIMS OF TREATMENT

Acute	Preventive
Goal: complete pain relief/improvement after 2 hours	Goal: to reduce the frequency and severity of attacks by at least 50%
Relief of associated symptoms	Reduce duration of attacks
Restoration of normal functioning	Improve responsiveness to acute therapy
Prevention of recurrence	Prevent medication overuse headache
Consistent efficacy in 2-3 attacks	Improve function and reduce disability
Sustained pain relief within 24 hours	

Giamberardino MA & Martelletti P. Expert Opin Emerg Drugs 2015;20:137

PATHOPHYSIOLOGY OF CHRONIC MIGRAINE

Chronic migraine: Headache occurring on **15 or more days** per month for **more than 3 months**, which **has the features of migraine headache** on **at least 8 days** per month.

Structural changes

- Periaqueductal gray (PAG) matter changes
- Iron deposition in certain areas of the brain (PAG)

Functional changes

- Focal changes in brain metabolism
- Hyperexcitability of the cortex
- Central sensitization

Pharmacologic changes

- Changes in excitatory amino acid levels and ratios in certain areas of the brain (anterior cingulate gyrus and insula)

MIGRAINE TRIGGERS

Sleep

- Too much sleep or too little sleep, and poor sleep quality can trigger migraine attack

Stress

- Migraine and stress are strongly linked

Food

- Skipping meals and fasting → hypoglycemia, dehydration
- Dietary products (chocolate, cheese, yoghurt), additives (MSG), caffeine, and alcoholic drinks.

Weather

- Barometric changes (high altitude), lightning, temperature, and precipitation

Sensory Stimuli

- Visual: light (sunlight/blinding light)
- Olfactory: odors like perfumes, paints, gasoline, bleach etc
- Noise

Hormonal Changes

- `Migraine is closely associated with female hormones. Some women find their migraines start at puberty, and are linked to their menstrual cycle.

Marmura, MJ. Triggers, Protectors, and Predictors in Episodic Migraine. *Current Pain dan Headache Reports*.2018;22:81
Hoffmann J and Recober A. Migrain and Triggers: Post hoc ergo propter hoc?.*Curr Pain Headache Rep*.2013;17(10): 1-11

EVALUATING MIGRAINE TRIGGER

- A trigger causes headache within 24 h >50% of the time
- Do not confuse triggers with the cause of headache
- Not all triggers act equally to provoke headache
- There may be a "load" factor
- The presence of multiple triggers or a combination of particular triggers may be needed to provoke headache

Patients should be advised to avoid known triggers if possible and counselled on lifestyle and stress management

American Headache Society. Brainstorm 2013. Available at: http://www.americanheadachesociety.org/assets/1/7/Book_-_Brainstorm_Syllabus.pdf. Accessed 04 December, 2014.

MIGRAINE ACUTE THERAPY

Table 1 Analgesics and non-steroidal anti-inflammatory drugs (NSAIDS) in migraine treatment

Substances	Dosages (mg)	Route(s) of administration	Maximum dosage per day (mg)	Level of recommendation
Acetylsalicylic acid (ASA)	325–650	Oral	4000	A
	300–600	Suppository		
	1000	Intravenous	4000	A
Ibuprofen	200–800 oral	Oral	3400	A
Naproxen sodium	250–750 oral	Oral	1250	A
Diclofenac	50–100 oral	Oral	150	
Paracetamol (acetaminophen)	325–1000	Oral	4000	A
	325–1000	Suppository	4000	
Metamizol (dipyrone)	250–1000	Oral	4000	B
	500–1000	Intravenous		
Phenazone	500–1000	Oral	4000	B
	500–1000	Suppository	4000	
Tolfenamic acid	200 mg	Oral	4000	B
ASA + acetaminophen + caffeine	250 + 200 + 50		2000 + 1600 + 400	B

Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. *Springerplus*. 2016;5:637. Published 2016 May 17. doi:10.1186/s40064-016-2211-8

MIGRAINE ACUTE THERAPY

Table 1. Therapy of acute migraine attacks with triptans.

Triptans			
Active ingredient	Dosage and route of application	Side effects (selected)	Contraindications (selected)
Sumatriptan	50 or 100 mg p.o. 25 mg Supp.[b] 10 or 20 mg nasal 6 mg s.c.	Feeling of constriction in the chest and neck, paresthesias of the extremities, feeling of cold	Inadequately treated hypertension, coronary heart disease, angina pectoris, myocardial infarction, M. Raynaud, peripheral arterial disease, TIA or stroke, pregnancy, lactation, serious hepatic or renal insufficiency, multiple vascular risk factors, concurrent treatment with ergotamine, within 2 weeks after withdrawal of a MAO-inhibitor (for rizatriptan: dose reduction to 5 mg if propranolol is taken)
Zolmitriptan	2.5 or 5 mg Tablet or ODT. p.o. 5 mg nasal	Sumatriptan s.c. additionally: Local reaction at the injection site	
Naratriptan[a] Rizatriptan Almotriptan[a] Eletriptan Frovatriptan	2.5 mg p.o. 5 or 10 mg (ODT) p.o. 12.5 mg p.o. 20 or 40 mg p.o. 2.5 mg p.o.	AEs in naratriptan, almotriptan and frovatriptan somewhat milder than for sumatriptan	

OTC: over the counter; TIA: transient ischemic attack; OTD: orally dissolving tablet.
[a]Available without prescription in Germany (prescription-free, OTC).
[b]Sumatriptan Supp available in Switzerland.

Guidelines by the German Migraine dan Headache Society and German Society of Neurology.*Clinical and Translational Neuroscience*.2019:1-40

MIGRAINE ACUTE THERAPY

Table 2. Anti-emetics in the therapy of acute migraine attacks.

Anti-emetics			
Active ingredient	Dose and route of application	Side effects (selected)	Contraindications (selected)
Metoclopramide	10 mg p.o. 10 mg rectal 10 mg i.m. or i.v.	Early dyskinetic syndrome, restlessness	Children and adolescents younger than 18 years, hyperkinesias, epilepsy pregnancy, prolactinoma
Domperidone	10 mg p.o.	Less frequent than for metoclopramide	Children under 12 years and under 35 kg BW, otherwise like metoclopramide, but less marked and rarer. QTc-time-prolongation, medications that prolong the QTc time.

BW: body weight.

Diener HC, Lee DH, Nagel S, Dresler T, Gaul C, Kuhn KH, et al. Treatment of Migrain attacks and prevention of migraine: Guidelines by the German Migraine dan Headache Society and German Society of Neurology.*Clinical and Translational Neuroscience*.2019:1-40

INIATING MIGRAINE PROPHYLAXIS

Consider and discuss prophylactic therapy with patient when:

- Quality of life, business duties, or school attendance are severely impaired
- Patient experiences ≥2 attacks month, duration >24 hours
- Migraine attacks do not respond to acute drug treatment/AE
- Frequent, very long, or uncomfortable auras occur

Migraine prophylaxis is regarded as successful if the frequency of migraine attacks per month is decreased by ≥50% within 3 months

EFNS = European Federation of Neurological Societies
Evers S *et al. Eur J Neurol.* 2009;16(9):968-81.

HOW TO START MIGRAINE PREVENTION THERAPY ?

- **Start the chosen drug at a low dose** and *increase it slowly* until therapeutic effects develop, the ceiling dose is reached, or adverse events become intolerable
- **Consider comorbidity** and *coexistent illnesses* in drug choice.
- Give each treatment an **adequate trial** (*2 to 6 months* before the maximal response to a treatment is evident.
- **Set realistic goals.** Success is defined *as a 50% reduction in attack frequency* or headache days, a significant decrease in attack duration, or an improved response to acute medication.
- **Reevaluate** therapy
- **Involve patients** in their care. Address patient expectations.

- Silberstein SD. Preventive Migrain Treatment. *Continuum (Minneap Minn).* 2015;21(4): 973-989

GOALS OF MIGRAINE PREVENTION THERAPY

- *Reduce* **attack** *frequency, severity, duration, and disability*
- *Improve* **responsiveness** to and avoid escalation in use of **acute treatment**
- *Improve* **function** and *reduce* **disability**
- *Reduce* **reliance** on *poorly tolerated, ineffective,* or unwanted **acute treatments**
- *Reduce* **overall cost** associated with migraine treatment
- *Enable* **patients** to *manage their own disease* to enhance *a sense of personal control*
- *Improve* health-related **quality of life**
- *Reduce* headache-related **distress and psychological** symptoms

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PHARMACOLOGICAL APPROACH

Table 4. Substances for migraine prevention with high/good scientific evidence.

Active substance	Dosage	Side effects (selected)	Contraindications (selected)
Propranolol	40–240 mg	F: fatigue, arterial hypotension	A: AV-Block, bradycardia, heart failure, Sick-Sinus-Syndrome, Asthma bronchiale
Bisoprolol	5–10 mg	S: insomnia, dizziness	R: Diabetes mellitus, orthostatic dysregulation, depression
Metoprolol	50–200 mg	S: hypoglycemia, bronchospasm, bradycardia, gastro-intestinal complaints, erectile dysfunction	
Flunarizine	5–10 mg	F: fatigue, weight gain S: gastro-intestinal complaints, depression R: Hyperkinesias, tremor, Parkinsonoid	A: focal dystonia, pregnancy, lactation, depression R: M. Parkinson in the family
Topiramate	25–100 mg	F: fatigue, cognitive impairment, weight loss, paresthesias S: impaired taste, psychosis, kidney stones, depression R: narrow-angle glaucoma	A: renal insufficiency, kidney stones, narrow-angle glaucoma R: depression, anxiety disorder, low body weight, anorexia
Valproic acid	500-1000 mg	F: fatigue, dizziness, tremor S: skin rash, alopecia, weight gain R: Impaired liver function	A: Impaired liver function, pregnancy (neural tube defects), women of childbearing potential, alcohol abuse
OnabotulinumtoxinA in chronic migraine	155–195 U i.m.	S: muscle diseases, undesired cosmetic effects, weakness of neck muscles	A: Myasthenia gravis R: Anticoagulation
Amitriptyline	50–75 mg	F: fatigue, dry mouth, dizziness, weight gain	A: Heart failure, glaucoma, prostate hypertrophy, -prostate adenoma

Side effects arranged by: F: frequent; S: sometimes; R: rare; Contraindications arranged by: A: absolute, R: relative

:Guidelines by the German Migraine dan Headache Society and German Society of Neurology.*Clinical and Translational Neuroscience.*2019:1-40

MECHANISMS OF ACTION

Beta Blocker	• Reduce adrenergic tone : presynaptic noradrenergic receptor blockade, reducing norepinephrine release and synthesis, inhibiting central beta-adrenergic receptors, and reducing the activity at the level of the adrenergic locus ceruleus.
Tricyclic antidepressants	• Inhibit norepinephrine and 5HT uptake. 5 The prevention of neurogenic inflammation may be mediated by a blockade of 5HT receptors and inhibition of arachidonic acid metabolism at the onset of a migraine attack.
Topiramate	• Blocks both calcium and sodium channels, inhibits excitatory glutamatergic receptors, and enhances GABA inhibitory activity. • Additionally, topiramate inhibits central activation of the trigeminal nucleus caudalis and upper spinal cord.
Valproate	• Increasing brain GABA → suppressing neurogenic inflammation via GABA-A receptors. • Modulates 5HT → uppressing the rostral brain stem modulator.

Estemalik E and Tepper S. 2008.Preventive treatment in migraine and the new US guidelines. *Neuropsychiatric Disease and Treatment*. 2013;9:709-720

SPECIAL SITUATIONS IN MIGRAINE PREVENTION

(migraine and comorbid disorders)

- **Depression:** amitriptyline (75–150 mg as first choice or alternatively venlafaxine (150–225 mg)
- **Anxiety disorder:** amitriptyline or venlafaxin
- **Epilepsy :** topiramate and valproic acid
- **Secondary vascular diseases** (stroke, coronary heart disease) : candesartan in arterial hypertension)

: Guidelines by the German Migraine dan Headache Society and German Society of Neurology.*Clinical and Translational Neuroscience*.2019;1-40

SPECIAL SITUATIONS IN MIGRAINE PREVENTION

(migraine and comorbid disorders)

- **Children:** *non-medical treatment should be preferentially used*
- **Pregnancy:** metoprolol, propranolol and amitriptyline.
- **Menstrually associated migraine:** Triptans or NSAIDs (short term for prevention)
- **Hemiplegic migraine:** lamotrigine or acetazolamide

Guidelines by the German Migraine dan Headache Society and German Society of Neurology.*Clinical and Translational Neuroscience*.2019;1-40

CGRP (CALCITONIN GENE-RELATED PEPTIDE) in MIGRAINE

- Studies **in the trigeminovascular system** revealed **that CGRP, a potent vasodilatory peptide** is involved in the headache pain occurring during a migraine attack.
- **CGRP plasma levels increase during migraine** and normalize after administration of triptans.
- Intravenous **infusion of CGRP : triggers migraine-like attacks**

Puledda F, Messina R, Goadsby PJ. An update on migraine: current understanding and future directions. *J Neurol*. 2017;264: 2031-2039

ERENUMAB

- Erenumab was monoclonal antibody (mAb) which **target the CGRP receptor.**
- **In episodic and chronic migrain:** erenumab administered subcutaneously at a monthly dose of 70 mg or 140 mg
- Reduced migraine frequency, the effects of migraines on daily activities, and the use of acute migraine specific medication over a period of 6 months → **potential therapy for migraine prevention.**

- Tepper S, Ashina M, Reuter U, Brandes JL, Dolezil D, Silberstein S, et al. Safety and Efficacy Erenumab for Preventive Treatmen of Chronic Migrain: a randomized, double blind, placebo-controlled trial phase 2 trial. *Lancet Neurol.* 2017;16:425-434

NON PHARMALOGICAL APPROACH

Non-pharmacological treatment is preferred in migraine when:

1. Pharmacological treatment is poorly tolerated
2. Inadequate or no response to pharmacological treatment
3. Medical contraindications for pharmacological treatment
4. Specific cases, such as pregnancy or lactation
5. Evidence of previous medication overuse
6. Considerable exposure to stress and inability to cope with stress.

Guidelines by the German Migraine dan Headache Society and German Society of Neurology.*Clinical and Translational Neuroscience.*2019;1-40

NON PHARMALOGICAL APPROACH

Behavioral Therapy

- Consist of: relaxation, thermal and electromyographic, biofeedback and cognitive behavioral therapy
- The aim are to teach patients to better cope with symptoms and identifying potential triggers for headache

Endurance Sports

- Regular endurance sport is frequently recommended in the prevention of migraine and is part of most multimodal therapy programs for headache patients

Puledda F and Shields K. Non-Pharmacological Approaches for Migraine. *Neurotherapeutics.* 2018; 15:336-345

TAKE HOME MESSAGE

- Migraine attack must be treated quickly, consistently and avoid recurrence.
- Many interdependent factor must be considered when treating patient with migraine.
- Prophylaxis of migraine is aiming to reduce frequency, severity, duration, improve responsiveness treatment of acute attack, improve function and reduce disability.
- Migraine prophylaxis is regarded as successful if the frequency of migraine attack per month is decreased by $\geq$ 50% within 3 months