

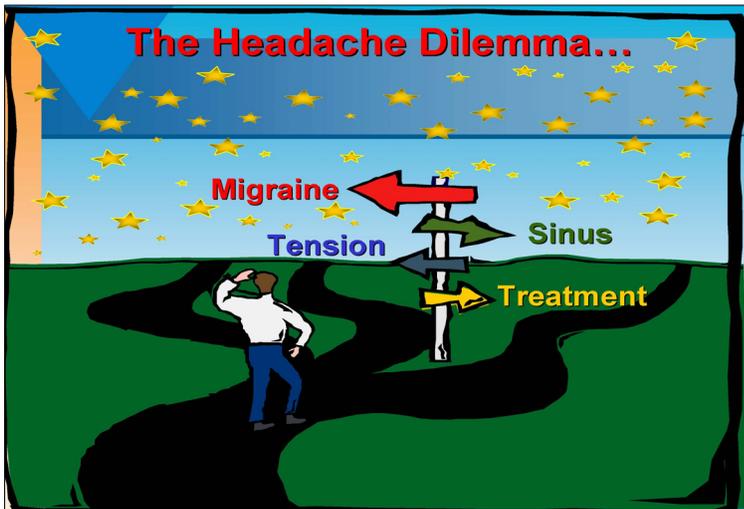
# 편두통과 긴장형 두통의 치료

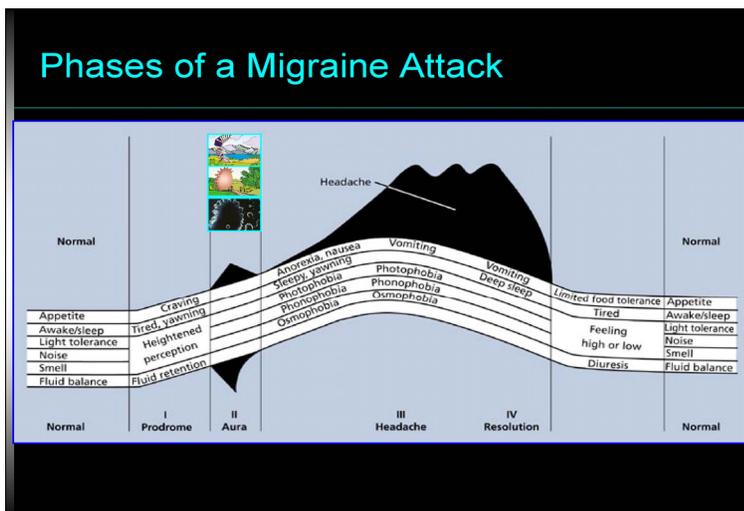
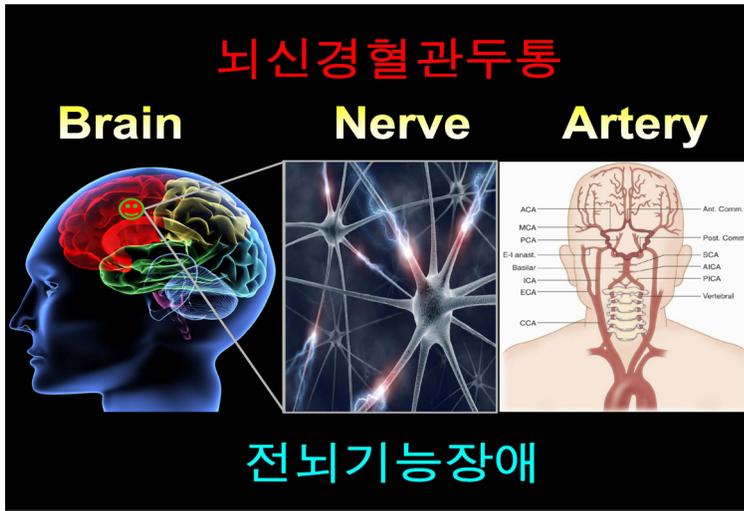


도진국  
대구가톨릭대학병원 신경과

## 두통강의

- 편두통
  - 급성 및 예방치료
- 긴장형두통
  - 급성 및 예방치료





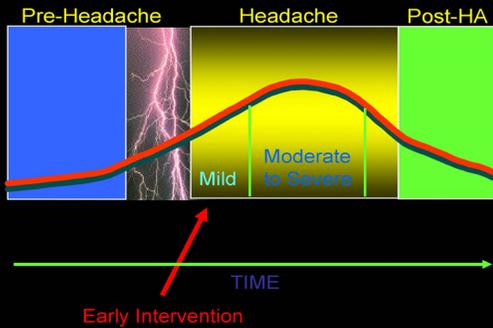
## 편두통의 치료



- 급성기 치료 Antiemetics!!
  - 1단계 - aspirin, acetaminophen, NSAIDs
    - caffeine 복합제제
  - 2단계 - triptans
  - 3단계 - ergot제제, phenothiazine, steroid
  - 4단계 - butalbital 제제, **Opioids x !!**
- 예방적 치료
  - 베타차단제 - propranolol, metoprolol, atenolol
  - 칼슘채널차단제 - flunarizine
  - 항우울제 - amitriptyline, venlafaxine
  - 항경련제 - valproate, topiramate
  - Candesartan, lisinopril... riboflavin and coenzyme Q10

## Acute treatment

*Fully functional state < 2hrs  
No recurrence < 24hrs*



## Acute treatment for migraine

- Nonspecific acute treatment
  - NSAIDs
    - Aspirin, ibuprofen, ketorolac, naproxen sodium...
  - Neuroleptics/antiemetics
    - Dopamine antagonists (prochlorperazine, metoclopramide, chlorpromazine)
    - Antihistamine (promethazine)
    - Serotonin antagonist (ondansetron)

**Table 4: Non-Steroidal Anti-Inflammatory Drugs: Pharmacokinetics and Dosage**

Drug	T <sub>max</sub> (hours)	Elimination half-life (hours)	Dose (mg)*	Dosage interval (if repeated) & maximum daily dose*
Acetylsalicylic acid (ASA) (tablet)	1 - 2	ASA: 0.25 Salicylate (active): 5-6 (after 1 g dose)	975 - 1,000	every 4-6 h; max: 5.4 g/day (varies depending on indication)
Acetylsalicylic acid (ASA)(effervescent)	~20 min	as above	975 - 1,000	every 4 h; max: 8 (325 mg) tablets
Ibuprofen (tablet)	1 - 2	2	400	every 4 h; max: 2,400 mg
Ibuprofen (solubilized)	< 1	2	400	every 4 h; max: 2,400 mg
Naproxen sodium**	2	14	500 - 550 (up to 825 mg)	twice a day; max: 1,375 mg
Diclofenac potassium (tablet)	< 1	2	50	3-4 times a day; max: 150 mg
Diclofenac potassium (powder for oral solution)	15 min	2	50	single dose recommended for migraine attack
Ketorolac (tablet)***	< 1	5	10	3-4 times a day; max: 40 mg

T<sub>max</sub> = time to maximum plasma concentration; \*Note: for acute migraine treatment, only one or two doses are usually recommended; doses are for adults; \*\*Absorbed more quickly than naproxen; \*\*\*No controlled trial evidence for efficacy in migraine

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## Acute treatment for migraine

### ■ Specific acute treatment

#### ● Triptans

- Intracranial vessel vasoconstriction : 5-HT<sub>1B</sub>
- Peripheral neuronal inhibition : 5-HT<sub>1D</sub>
- Presynaptic dorsal horn stimulation : 5-HT<sub>1D</sub>
- Enhance descending inhibitory pain path
- Influence 5-HT<sub>1F</sub>

#### ■ Ergots

**Table 6: Triptans - pharmacokinetics<sup>19,23,29,31,38,48</sup>**

	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Somatriptan	Zolmitriptan
Bioavailability	70%	50%	Males: 20% Females: 30%	Males: 63% Females: 74%	45%	SC: 96% Oral: 14% Nasal: 16%	Oral: 40% Nasal: 41%
T <sub>max</sub>	1 - 3 h	1 - 2 h	2 - 4 h	2 - 3 h	Oral: 1 - 1.5 h ODT: 1.6 - 2.5 h	SC: 15 min Oral: 2.5 h Nasal: 1 - 1.5 h	Oral/ODT: 2 h Nasal: 2 h
Onset	0.5 - 2 h	0.5 - 1 h	precise data not available; slow onset for most patients	1 - 3 h	0.5 - 1 h	SC: 10 - 15 min Oral (fast dissolving): 30 min, Nasal: 15 min	Oral/ODT: 45 min Nasal: 10 - 15 min
Elimination half-life	3 - 4 h	3.8 h	~26 h	5 - 8 h	2 - 3 h	2 h	2.5 - 3 h
Metabolism & elimination	MAO-A, CYP3A4, CYP2D6; inactive metabolites; 40% unchanged in urine	CYP3A4; active N-demethylated metabolite; 90% non-renal clearance	CYP1A2; several metabolites; active desmethyl frovatriptan	CYP 450 (various isoenzymes); inactive metabolites; 50% unchanged in urine	MAO-A; inactive & one active metabolites; 8 - 16% unchanged in urine	MAO-A; inactive metabolites	CYP1A2, MAO-A; inactive & one active metabolites; 8% unchanged in urine
Significant drug interactions*	None	CYP 3A4 inhibitors: E contraindicated within 72 h of potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole)	None (CYP1A2 inhibitors have minimal potential to affect kinetics of frovatriptan)	None	MAOIs (avoid use within 14 days)  Propranolol (↑ AUC of R; max. 5 mg single doses & 10 mg/24 h of R)	MAOIs (avoid use within 14 days)	MAOIs (avoid use within 14 days)  CYP 1A2 inhibitors (e.g., trimethoprim, fluvoxamine, ciprofloxacin): ↑ AUC & t <sub>1/2</sub> of Z; max. 5 mg/24 h of Z)

\* All triptans: do not use within 24 hours of an ergot derivative (e.g., ergotamine, DHE) or another triptan (due to possibility of additive vasoconstriction); there is a theoretical possibility of serotonin syndrome (rare) when combined with other serotonergic drugs (e.g., SSRIs, lithium) - however, this is controversial; AUC = area under the curve; MAOI = monoamine oxidase inhibitor; E = eletriptan; R = rizatriptan; Z = zolmitriptan; ODT = orally disintegrating tablet

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## Options for inadequate acute Tx

- Change dose or formulation
- Treat early when headache is mild
- Add adjunctives (NSAIDs)
- Add preventive therapy
- Screen for caffeine or other acute medication overuse
- Screen for medications (promote headache)

	Clinical Phenotype	Strategy	Medications
Increasing migraine severity - Refractoriness to therapy  	Mild – moderate attack strategies	1.a Acetaminophen	Acetaminophen ± metoclopramide
		1.b NSAID	Ibuprofen, diclofenac potassium, naproxen sodium, ASA, all ± metoclopramide
	Moderate – severe attack /NSAID failure strategies	2.a NSAID with triptan rescue	NSAID ± metoclopramide + a triptan later for rescue if necessary
		2.b Triptan	Triptan ± metoclopramide Sumatriptan (SC injection, nasal, oral) Zolmitriptan (nasal, oral, wafer) Rizatriptan (oral, wafer) Naratriptan (oral) Eletriptan (oral) Almotriptan (oral) Frovatriptan (oral)
	Refractory migraine strategies	3.a Triptan – NSAID combination	Triptan + NSAID taken simultaneously ± metoclopramide
		3.b Triptan – NSAID combination with rescue	Triptan + NSAID taken simultaneously ± metoclopramide + one or more for rescue later (as necessary) of: Ketorolac IM Indomethacin (oral or rectal) Prochlorperazine (oral or rectal) Chlorpromazine (oral) Dexamethasone or prednisone Opioid combination analgesic
3.c Dihydroergotamine		Dihydroergotamine (nasal or SC or IM self-injection) ± metoclopramide	

Clinical phenotype / strategy	Medication options
Vasoconstrictor unresponsive or contraindicated strategy	1. One of: acetaminophen, ibuprofen, diclofenac potassium, naproxen sodium, or ASA, all ± metoclopramide 2. Combinations of acetaminophen, ASA, and caffeine (note: combination product not available in Canada but can use individual components) ± metoclopramide 3. One or more of: ➤ ketorolac IM (self-injection) ➤ indomethacin (oral or rectal) ➤ prochlorperazine (oral or rectal) ➤ chlorpromazine (oral) ➤ dexamethasone or prednisone (short course) ➤ opioid (including tramadol) combination analgesics (monitor use closely) 4. One of: butalbital-containing analgesics, or butorphanol nasal spray (both: exceptional circumstances only – monitor use closely)
Menstrual migraine strategy	1. Acute therapy: General strategies 1 through 3c 2. Short term prophylaxis with one of: frovatriptan, zolmitriptan, naratriptan, or naproxen (frovatriptan recommended) 3. Short term prophylaxis with percutaneous estrogen 4. Continuous oral contraceptives (observe contraindications) 5. Less proven options for short term prophylaxis: magnesium, mefenamic acid
Migraine during pregnancy strategy	Avoid medication where possible 1. acetaminophen ± metoclopramide 2. acetaminophen with codeine ± metoclopramide 3. ibuprofen (avoid 1 <sup>st</sup> trimester and at /after 32 <sup>nd</sup> week gestation) ± metoclopramide 4. sumatriptan (if benefits outweigh risks – limited data but relatively safe) ± metoclopramide
Migraine during lactation strategy	Avoid medication where possible 1. acetaminophen ± metoclopramide 2. ibuprofen ± metoclopramide 3. sumatriptan ± metoclopramide 4. morphine (exceptional circumstances only - avoid high doses, maternal sedation, avoid when infant is premature, and use caution if infant under 1 month of age)

## Migraine prevention : When?

- > 3 / month
- Significant decreased daily activity
- Acute Tx's : ineffective, contralx, or overused
- Adverse effect of acute medications
- Patient preference
- Special circumstances: elderly, pediatric and pregnant pts

## General rules for prevention

- Slowly titrate
- Adequate durations (2-3 months)
- Consider
  - drug interactions/contraindications
  - comorbid conditions (epilepsy, HTN)
  - combinations for refractory pts
- Headache diary
- Taper when headaches are controlled

Table 1. Classification of migraine preventive therapies (available in the United States)

Level A: Medications with established efficacy (≥2 Class I or ≥2 Class II studies)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level D: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as possibly or probably ineffective
Antiepileptic drugs <b>Divalproex sodium</b>	Antidepressants/SSRI/SSNRI/TCA <b>Amitriptyline</b>	ACE inhibitors <b>Lisinopril</b>	Carbonic anhydrase inhibitor Acetazolamide	Established as not effective Antiepileptic drugs
<b>Sodium valproate</b>	Verapamil	Angiotensin receptor blockers <b>Candesartan</b>	Antithrombotics Acetazolamide	<b>Lamotrigine</b>
<b>Topiramate</b>	β-Blockers Atenolol*	α-Agonists Clonidine*	Acenocoumarol	Probably not effective Clomipramine*
β-Blockers <b>Metoprolol</b>	Nadolol*	Guafacine*	Coumadin	Possible not effective Picotamide
<b>Propranolol</b>	Triptans (MRM) <sup>†</sup>	Antiepileptic drugs	Picotamide	Probably not effective Acetubolol*
<b>Timolol</b>	Naratriptan <sup>‡</sup>	Antidepressants SSRI/SSNRI	Antidepressants SSRI/SSNRI	
Triptans (MRM) <sup>†</sup>	Zelmitriptan <sup>‡</sup>	Carbamazepine*	Fluoxetine*	Clonazepam*
Flunarizine <sup>‡</sup>		β-Blockers Nebivolol	Fluoxetine	Nabumetone*
		Pindolol*	Antiepileptic drugs <b>Valproic acid</b>	Oxcarbazepine
		Anticholinergics Cyclopropridine	TCA's Protriptyline*	Teicoplanin
			β-Blockers Bisoprolol*	
			<b>Ca<sup>2+</sup> blockers</b>	
			Nicardipine*	
			Nifedipine*	
			Nimodipine	
			Verapamil	
			Direct vascular smooth muscle relaxants Cyclandolate	

Abbreviations: ACE = angiotensin-converting-enzyme; MRM = menstrually related migraine; SSNRI = selective serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.  
\* Classification based on original guideline and new evidence not found for this report.  
† For short-term prophylaxis of MRM.

Guideline	Acute treatment	Prophylactic treatment	Other issue
AHS/AAN	<ol style="list-style-type: none"> <li>1. Triptans</li> <li>2. Ergots</li> <li>3. NSAIDs</li> <li>4. Combination analgesics</li> <li>5. Barbiturates (butalbital...)</li> <li>6. Opiates</li> </ol> Rescue tx ; corticosteroids	<ol style="list-style-type: none"> <li>1. Di(valproates)</li> <li>2. Topiramate</li> <li>3. Beta-blockers (metoprolol, Propranolol)</li> </ol> Amitriptyline, Venlafaxine, Atenolol, Nadolol, Lisinopril, Candesartan...	MRM : Frovatriptan, Naratriptan, Zolmitriptan Level C : fluoxetine, gabapentine, protriptyline, Nimodipine, Verapamil
EFNS/NICE	<ol style="list-style-type: none"> <li>1. Oral triptan and NSAID</li> <li>2. Oral Triptan</li> <li>3. Aspirin or paracetamol</li> </ol> + Metopramide or prochlorperazine Non-oral NSAID or triptan Do not offer ergots or opioids	Antiepileptics; Valproate, Topiramate + beta-blockers; Metoprolol, Propranolol Calcium channel blockers; Flunarizine *Level B : amitriptyline, Venlafaxine, Naproxen... *Level C : ASA, Candesartan...	<ol style="list-style-type: none"> <li>1. Menstrual-related : frovatriptan or Zolmitriptan</li> <li>2. During pregnancy paracetamol for Acute</li> </ol>
Canadian	<ol style="list-style-type: none"> <li>1. Triptans &amp; Ergots</li> <li>2. ASA/NSAIDs</li> <li>3. Opioids &amp; tramadol</li> </ol> Anti-emetics	Strong Recommend ; <ol style="list-style-type: none"> <li>1. Topiramate, propranolol, metoprolol, amitriptyline</li> <li>2. nadolol, gabapentin, Candesartan...</li> <li>3. riboflavin, CoQ10, magnesium</li> </ol> Weak Recommend ; <ol style="list-style-type: none"> <li>1. divalproate, flunarizine</li> <li>2. Venlafaxine, lisinopril</li> </ol>	During pregnancy & lactation; Magnesium, beta-blocker (propranolol or Metoprolol) → amitriptyline

## Alternatives

- Modifications
  - Regular sleep, meals and exercise
  - Avoid high carbohydrates
  - Adequate hydration
  - Caffeine restriction
- Physical therapy
  - Isometric neck exercise
- Dietary
  - Magnesium, Coenzyme Q10, Rivoflavin
- .....





## Preventive Treatment (Chronic TTH)

### Non-Pharmacologic

- Proper sleep hygiene
- Stress management
- Acupuncture
- EMG-Biofeedback
- Physical therapy

### Pharmacologic

- TCAs (best efficacy)
  - Amitriptyline...
- SNRI & SSRIs (better tolerated)
  - Mirtazapine, Extended-release venlafaxine

## What type of doctor should you see?

Family physician, internal medicine specialist

### Primary Care

Ask for a specific headache appointment and get a specific diagnosis

May need referral from primary care

### Neurologist

Headaches frequent and difficult to manage or if there are other medical conditions to manage simultaneously

Headaches are severe and disabling; may need referral

### Headache Specialist

Headaches not responsive to routine care; other existing medical conditions making treatment plan complex