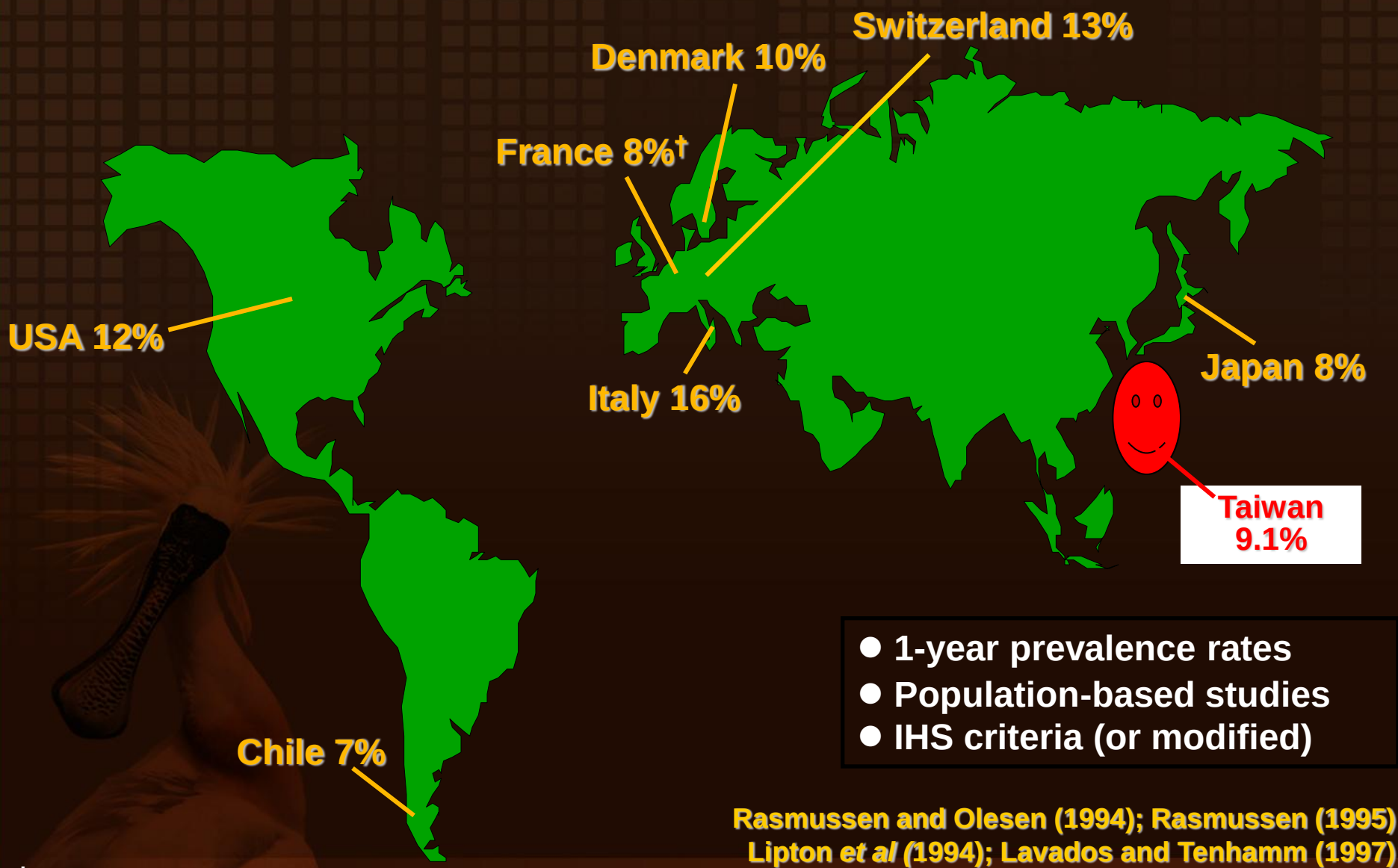
Update in acute and preventive treatment of migraine

偏頭痛之急性及預防性治療準則

奇美醫學中心
神經內科
林高章醫師

偏頭痛的世界盛行率



- 1-year prevalence rates
- Population-based studies
- IHS criteria (or modified)

Rasmussen and Olesen (1994); Rasmussen (1995); Lipton *et al* (1994); Lavados and Tenhamm (1997); Sakai and Igarashi (1997)

†Prevalence measured over a few years

Migraine in Asia

Headache
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Research Submission

Migraine Disability Awareness Campaign in Asia: Migraine Assessment for Prophylaxis

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Headache 2008;48(9):1356-65.

- 8 countries, 144 clinics, 244 neurologists participated.
- F:M=72:28 (%)
- 2782 pts enrolled, 66% have migraine.
- ~4.9 severe headache/ per month.
- 65 % missing school, work…,etc.
- 87% took acute abortive Rx.
- 68.2% needed for preventive therapy by Drs suggestion (only 29.2% took preventive therapy)

Conclusions.—Migraine is the most common headache diagnosis in neurological services in Asia. The prevalence of migraine was higher in countries with higher referral rates of patients to neurological services. Migraine remains under-diagnosed and under-treated in this region even though a high disability was found in patients with migraine. Probable migraine was adopted into the migraine diagnostic spectrum by neurologists in this study.

Headache 2008;48(9):1356-65.

Migraine Without Aura (ICHD, 2004)

- At least two of the following features:
  - Unilateral location
  - Throbbing character
  - Worsening pain with routine activity
  - Moderate to severe intensity

2

- At least one of the following features:
  - Nausea and/or vomiting
  - Photophobia and phonophobia

1

- Medical History, Headache diary, Migraine triggers
- Investigations (only to exclude secondary causes)
  ex: EEG / CT Brain / MRI

1

Frequency $\geqq$5 times, duration~ 4-72 hours

台灣經驗
(755 headache patients, 102 neurologists)

ORIGINAL ARTICLE

Diagnosis and Development of Screening Items for Migraine in Neurological Practice in Taiwan

Shuu-Jiun Wang,[1] Jong-Ling Fuh,[1] San-Yong Huang,[2] Sheng-Shan Yang,[3] Zin-An Wu,[1] Chang-Hung Hsu,[4] Chi-Hong Wang,[5] Hsiang-Yu Yu,[1] Po-Jen Wang,[6] on behalf of the Taiwan MAP Study Group†*

中重度頭痛、噁心、畏光
敏感性 82%，特異性 73%
陽性預測率=91%(神經科門診)

J Formos Med Assoc 2008;107:485–94

1. In past 3m, does your HA have nausea?
2. Do you have more light sensitive during HA?
3. Do you have more disability during HA?

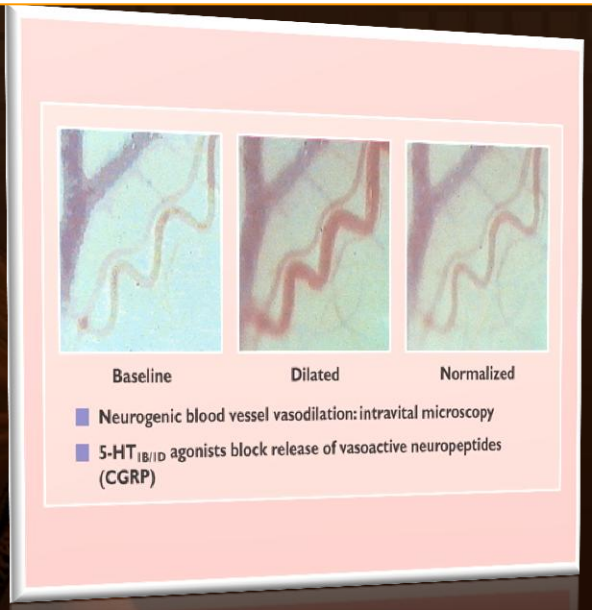
2/3==91%
3/3==98% **(Lipton et al, Neurology, 2004)**

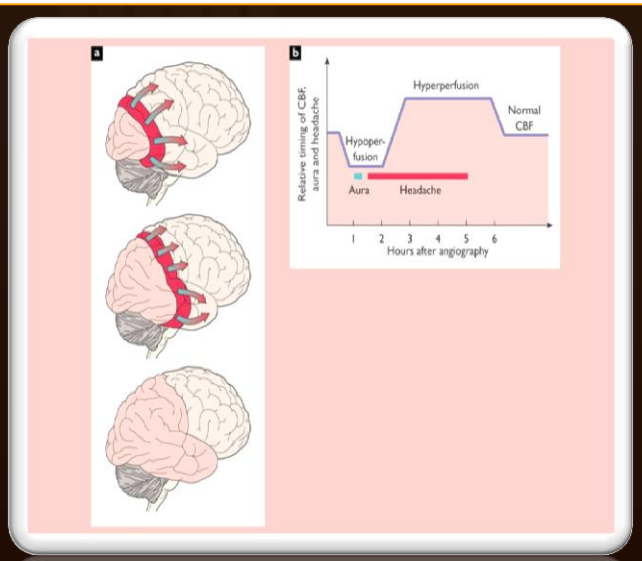
 Published by Wiley Periodicals, Inc.

Review Article **(2011)**

One Hundred Years of Migraine Research: Major Clinical and Scientific Observations From 1910 to 2010

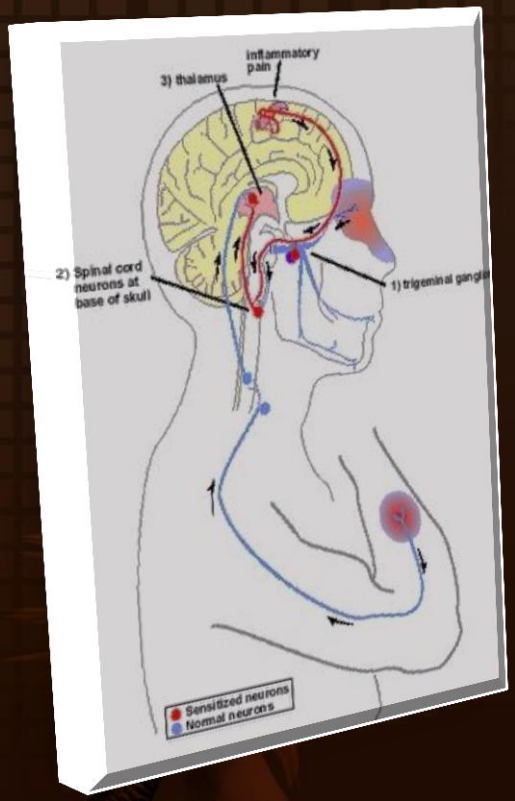
Peer C. Tfelt-Hansen, MD, PhD; Peter J. Koehler, MD, PhD





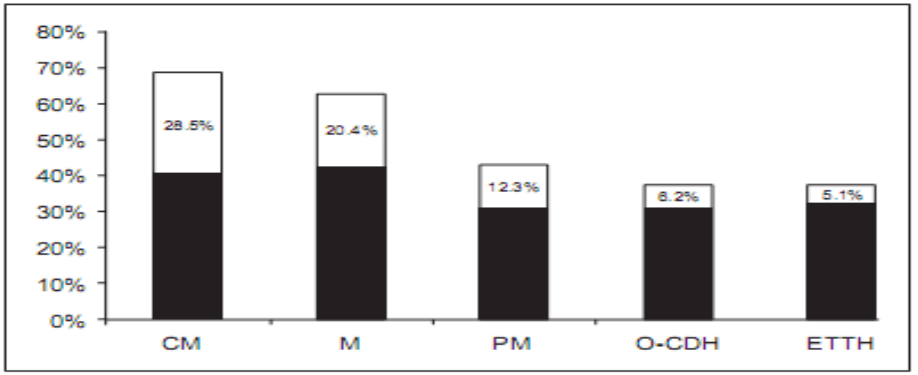
Presumed mechanism from Extracranial -vascular to Trigeminal-vascular theory to Central theory

Central Sensitization and Cutaneous Allodynia



- 80% of migraine patients experienced ***cutaneous allodynia*** during attacks due to central sensitization
- More frequent of allodynia, more easily develop to chronic migraine

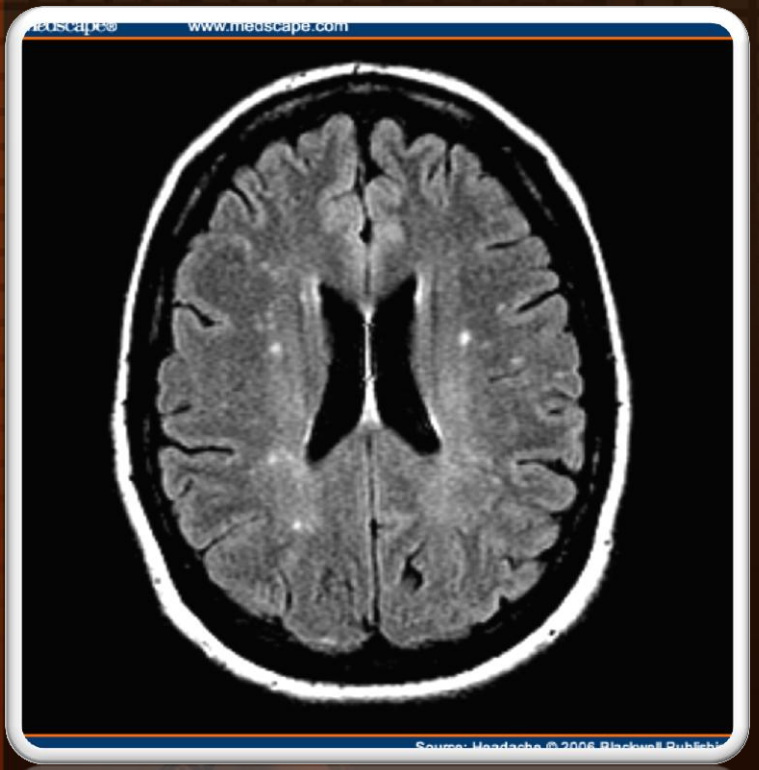
Figure 3 Relative frequency and severity of cutaneous allodynia according to the headache subtype



CA, cutaneous allodynia; CM, chronic migraine; M, migraine; PM, probable migraine; O-CDH, other chronic daily headaches; ETTH, episodic tension-type headache; □, severe CA; ■, mild/moderate CA. Adapted from [39•].

Burstein R et al. *Ann Neurol*. 2000;47:614-624;
Burstein R et al. *Headache*. 2002;42:390-391.
Bigal and liton et al. Headche. 2009;22::269-276.

Imaging study in migraineurs



1. Increased frequency of stroke and white matter hyperintensities in migraine

2. Migraineurs with one of risk factors (HTN, DM, dyslipidemia, etc) had more stroke risks for 2~3x (CI 1.3~9.6) than non-migraineurs

3. With aura had higher incidence

1. EFNS-2011, Budapest Congress
2. Chang et al. BMJ, 1999

Migraine and Stroke: Review

	Etminan et al[28]	Schurks et al[29]	Spector et al[30]
Overall migraine			
All studies	2·16 (1·89–2·48)	1·73 (1·31–2·29)	2·04 (1·72–2·43)
Case-control studies	2·18 (1·86–2·56)	1·96 (1·39–2·76)	..
Cohort studies	2·10 (1·61–2·75)	1·47 (0·95–2·27)	..
Women	..	2·08 (1·13–3·84)	..
Men	..	1·37 (0·89–2·11)	..
Women and men <45 years	2·36 (1·92–2·90)	2·65 (1·41–4·97)	..
Women <45 years	2·76 (2·17–3·52)	3·65 (2·21–6·04)	..
Oral contraceptive use	8·72 (5·05–15·05)	7·02 (1·51–32·68)	..
Smoking	..	9·03 (4·22–19·34)	..
Migraine with aura	2·27 (1·61–3·19)	2·16 (1·53–3·03)	2·25 (1·53–3·33)
Smoking	..	1·5 (1·1–2·3)*	..
Women currently using oral contraceptives and smoking	..	10·0 (1·4–73·7)*	..
Migraine without aura	1·83 (1·06–3·15)	1·23 (0·90–1·69)	1·24 (0·86–1·79)

Summary of the relative risk (95% CI) between migraine and ischaemic stroke in three meta-analyses of observational studies. ..=not reported. *Estimate provided by only one study.

Table: Migraine and the risk of ischaemic stroke

Conclusion:

MO is not a risk for stroke, MA doubled stroke risk especially in young female

MO=migraine without aura
MA=migraine with aura

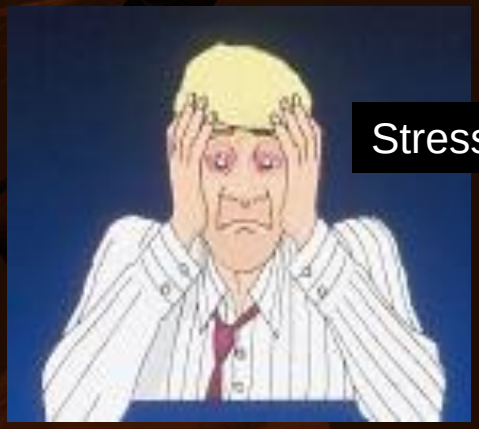
(Lancet Neurology, 2012)

Triggering the triggers

Changes in sleep habit

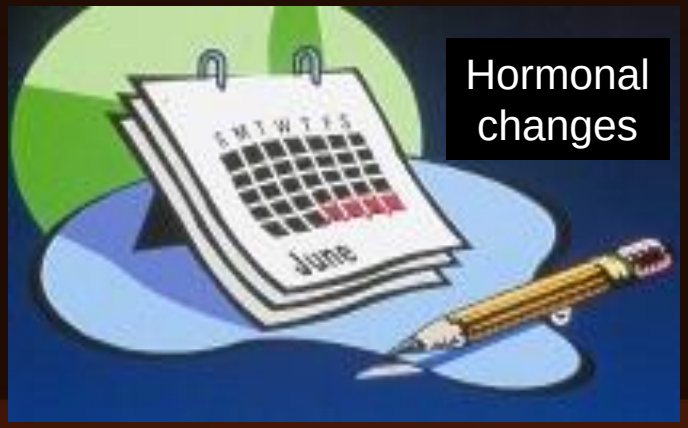
Weather

Alcoholic beverages

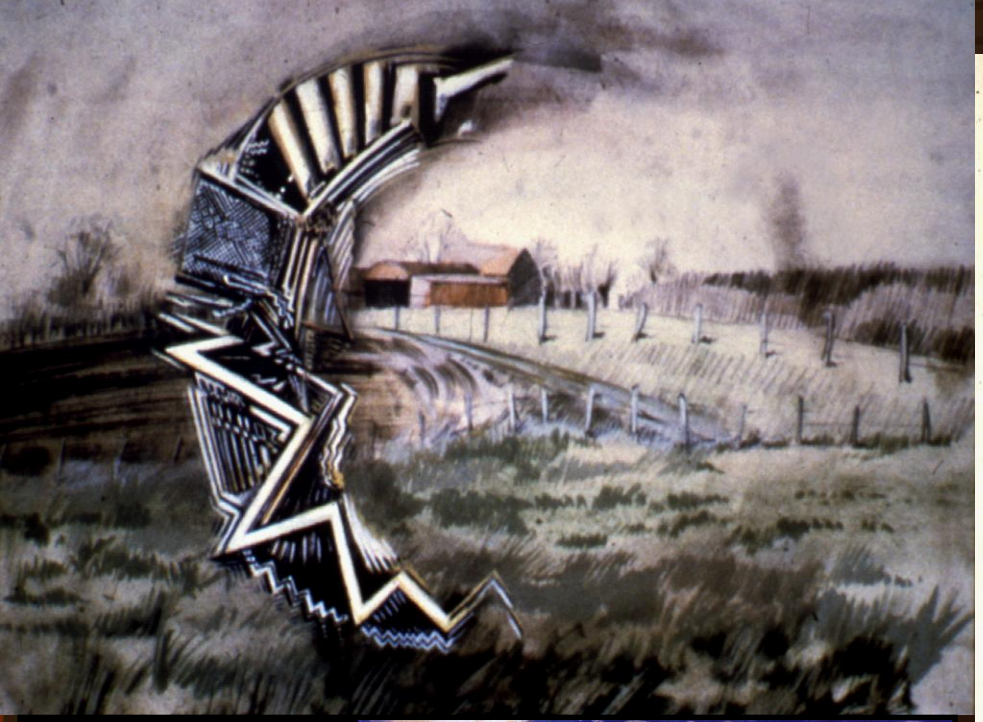


Stress

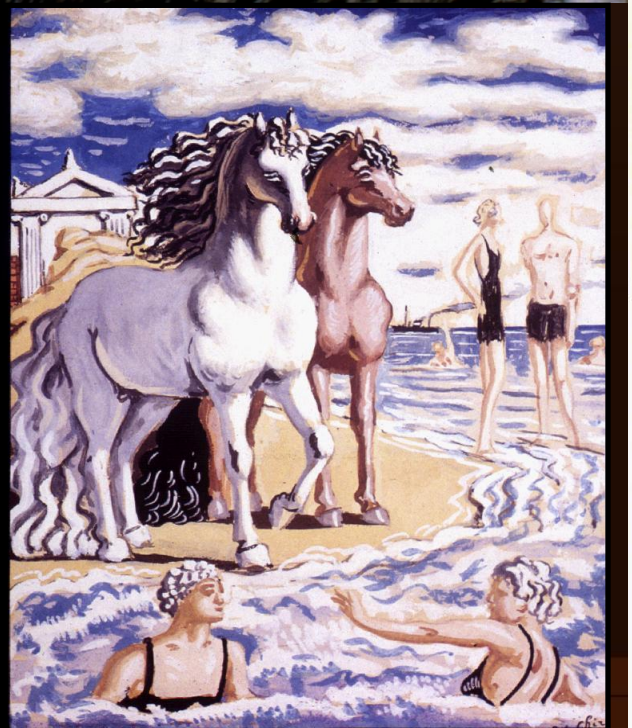
Glare or flickering light



Hormonal changes



Teichopsia



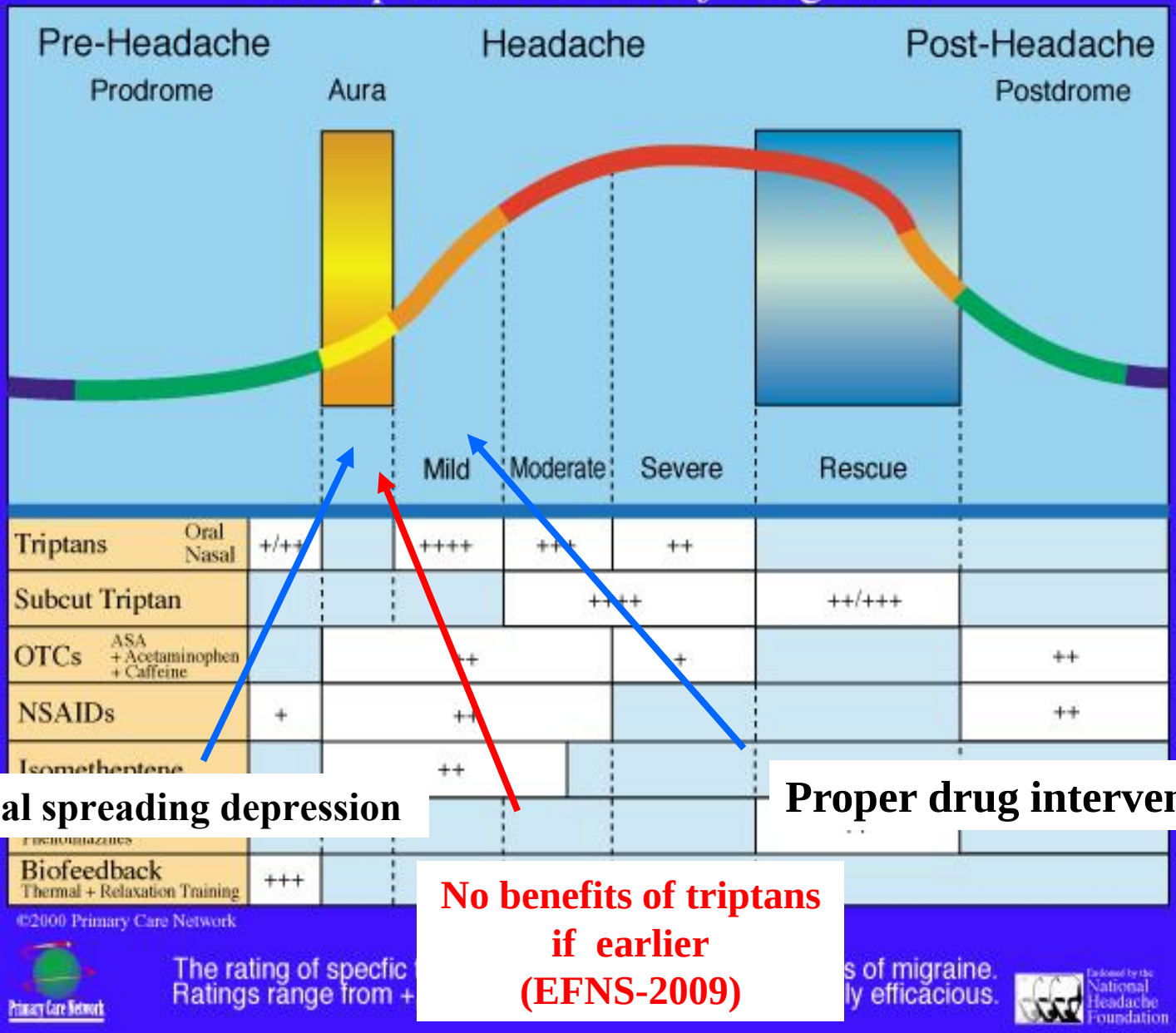
Prima uisio tercie partis.

Ecce homo
sumpta
abalius
homini
uus qu
ñ sū dig
na nom

nari homo ppt̄ trīsgressionē legis
dī. cū deberem ee nulla & sum inutili
ñ qđ dī creatura sum ipsī grā. qui
me etiā saluabit. uidi adorientem
& ecce illuc conspexi uelut lapidem
unū totū integrū unīusq; latitudi
nis atq; altitudinis habentē ferre
colorē. & sup ipsum candidā nubē
ac sup ea positū regalem tronum r
tundū. in quo sedebat quidā uiue
luciduſ mirabilis gl̄ē. tantiq; clari
tis ut nullatenꝰ eū pspicue posse
ūtueri. habens qđ in pectore suo li
mū nigrū & luculentū. tantę lati
tudinis ut alicui magno hominis
pectuſ ē. circūdatū lapidib; pciosis
atq; margaritis. Ex de ipso lucido
sedente tr̄rono prendebat magnus
circuluſ aurei coloris ut aurora. cui
amplitudinē nullom̄ cōphendere
potuī. quanꝰ ab oriente ad septen
nē & ad occidentē atq; ad meridiem

Alice in Wonderland (migraine aura)

Therapeutic Phases *of* Migraine



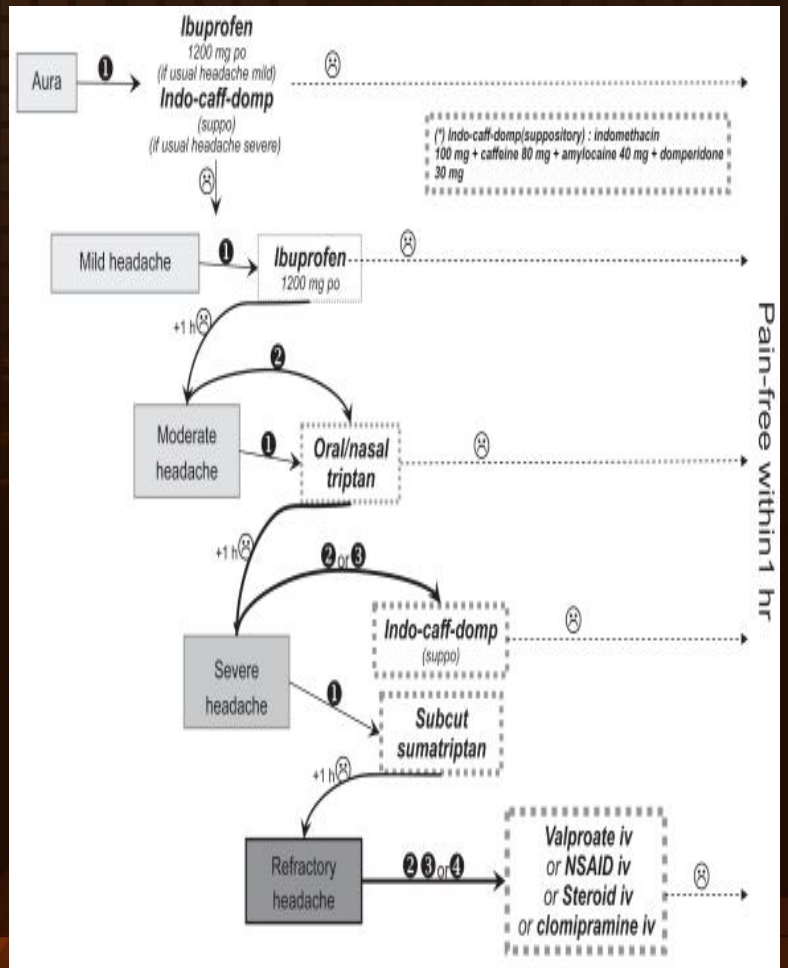
Cortical spreading depression

Proper drug intervene

No benefits of triptans if earlier (EFNS-2009)

Guideline for acute migraine

Stepwise care (EHF, UK, Scotland)



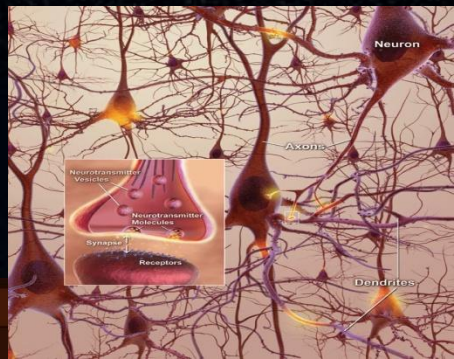
- **Advantage: Simple, clear, fast**
- **Disadvantage: time-dependent to effectiveness**

Guideline for acute migraine

Stratified Care (EFNS, Italy, US, Taiwan)

Mild to moderate Headaches (MIDAS grade I or II)	→ ASA, NSAIDs (PO or IM) 複方止痛藥，DHE, Ergotamine
Moderate to severe Headaches (MIDAS grade III or IV)	→ Triptans (PO or nasal spray) , DHE, Butorphanol (Stadol®) , anti-dopaminergics, Dexamethasone, NSAIDs

(Taiwan Headache Society-2007)


Neuron
Axons
Neurotransmitter Vesicles
Neurotransmitter Molecules
Synapse
Receptors
Dendrites

Evidences based on

- Scientific effects measures (+++,++,+,0).
- Clinical impression of effects (+++.++,+,0)
- Quality of evidence (A,B,C)

- Technical Reviews by AHCPR (Agency for Health Care Policy and Research).
- US Headache Consortium (AAN, AAFP,AHS,ACEP,ACP-ASIM, AOA, NHF).
- The Cochrane Collaboration Review.
- BASH and MIPCA.

Clinical guidelines and continuing education credit.

Quality of evidence (A,B,C)

A Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings.

B Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal.

C The US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials.

Groups of Recommendation in acute and preventive treatment (US headache consortium)

1 High efficacy, mild to moderate ADE.

2 Low efficacy, moderate improving, limited numbers studied, reported conflicting results.

3 Based on opinions, not RCT, mild to moderate AD E, frequent Severe ADE.

4 With proven efficacy, but with frequent severe ADE.

5 Proven to have limited or no efficacy.

Evidence-based acute therapies for migraine (US)

1. **Sumatriptan (po, iv, sc)**
2. **Rizatriptan (po)**
3. **Naprosin solium (po)**
4. **Ibuprofen (po)**
5. **Prochlorperazine**

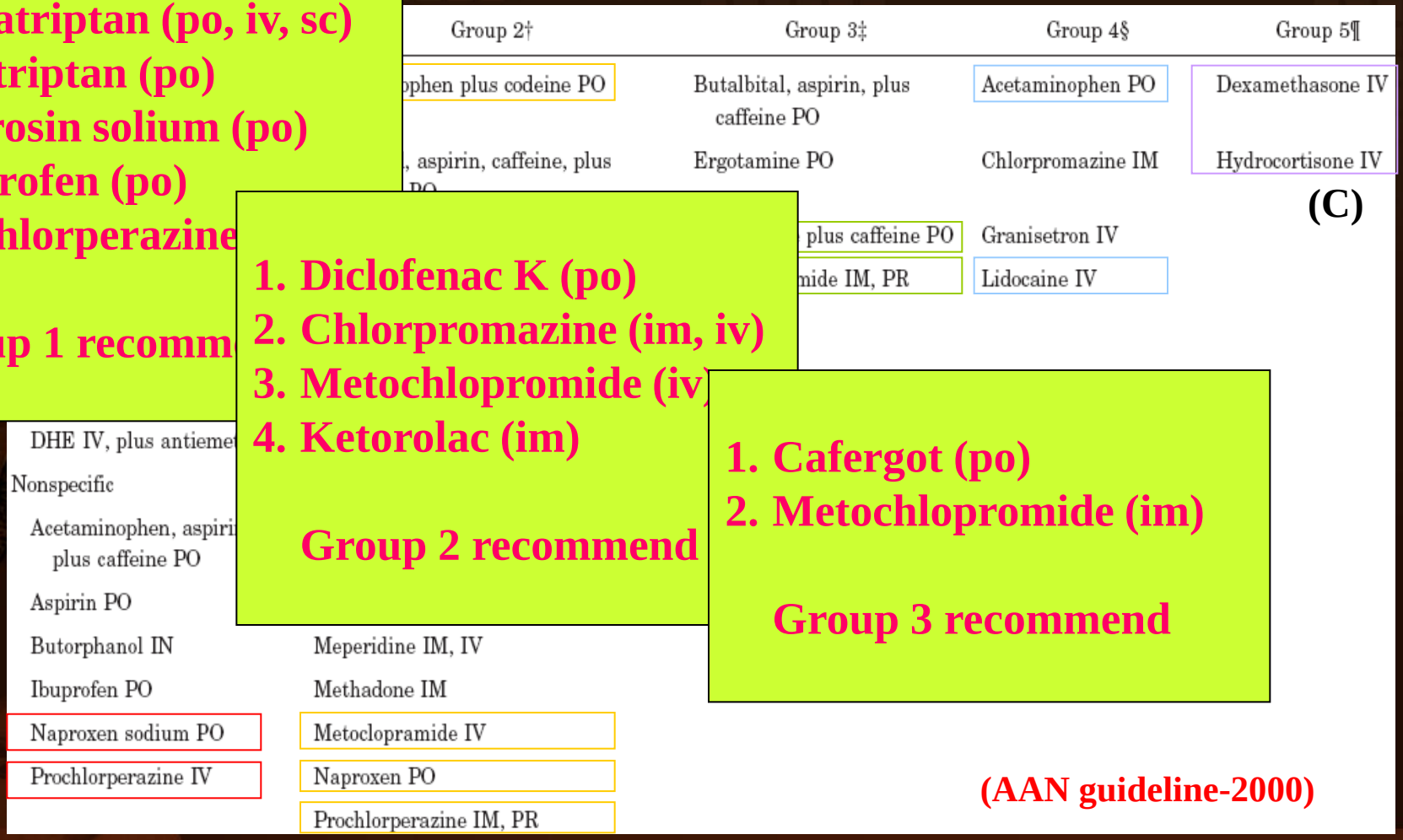
Group 1 recomm

1. **Diclofenac K (po)**
2. **Chlorpromazine (im, iv)**
3. **Metochlopromide (iv)**
4. **Ketorolac (im)**

Group 2 recommend

1. **Cafergot (po)**
2. **Metochlopromide (im)**

Group 3 recommend



	Group 2†	Group 3‡	Group 4§	Group 5¶
	ophen plus codeine PO	Butalbital, aspirin, plus caffeine PO	Acetaminophen PO	Dexamethasone IV
	, aspirin, caffeine, plus PO	Ergotamine PO	Chlorpromazine IM	Hydrocortisone IV
		plus caffeine PO	Granisetron IV	
		mide IM, PR	Lidocaine IV	
DHE IV, plus antieme				
Nonspecific				
Acetaminophen, aspiri plus caffeine PO				
Aspirin PO				
Butorphanol IN	Meperidine IM, IV			
Ibuprofen PO	Methadone IM			
Naproxen sodium PO	Metoclopramide IV			
Prochlorperazine IV	Naproxen PO			
	Prochlorperazine IM, PR			

(C)

(AAN guideline-2000)

表二、偏頭痛各種急性治療藥物的治療建議

藥物種類	在急性偏頭痛治療中的主要角色	推薦等級*	臨床療效**
Triptan			
sumat			
sumatriptan (im)	中重度偏頭痛或第一線治療無效之輕中度偏頭痛，尤其是嚴重噁心嘔吐或需非腸道給藥途徑時	A	+++
Er			
ergotamine/caffeine (po)	中重度偏頭痛或第一線治療無效之輕中度偏頭痛	B	++
dihydroergotamine (po)	同上	B	++
Simple analgesics			
ac			
di			
(im)	第一線治療。		
NSAIDs			
ketorolac (im, iv)	急診使用	B	++
aspirin (po)	輕中度偏頭痛的第一線治療	A	++
ibuprofen (po)	輕中度偏頭痛的第一線治療，兒童患者的第一線治療	A	++
diclofenac (po), tolfenamic acid (po), naproxen (po), ketoprofen (po)	輕中度偏頭痛的第一線治療	B	++

Taiwan guideline for Acute Rx (2007)

(A) Imigran (po+ inha), Aspirin, Ibuprofen

(B) Ergots, DHE, Panadol, NSAID (po/im)

Antiemetics			
prochlorperazine (im)	其他急性治療之輔助用藥，有止吐效果。	B	++
(B) Primperan, Novamin, Droperidol (im/iv)			
droperidol (iv)	同上，但不良反應率高且嚴重，重積狀態可考慮使用。	B	++
Others			
steroids (iv) (dexametha-sone, hydrocortisone,	配合多巴胺拮抗劑使用，可作為偏頭痛重積狀態的救援治療	B	++
(C) Magesium,Valproate, Lidocaine, Opioids			
lidocaine (in)	未定	C	?
valproate (iv)	未定	C	?
opioids	僅限救援治療或孕婦的末線用藥，宜保守使用，避免成癮。	C	++

po = per os; iv = intravenous; im = intramuscular; in = intranasal

*推薦等級 (Strength of recommendation)—Grade A: 已有多個設計嚴謹、隨機分派的臨床試驗針對推薦事項獲得一致發現；Grade B: 已有幾個隨機分派的臨床試驗支持推薦項目，但此科學性的支持性不夠嚴謹。例如，只有零星幾個相關的試驗存在，或這些既有的試驗結論不完全一致，或者，這些試驗的結論與推薦事項並非完全相符。Grade C: 目前尚無相關的隨機分派臨床試驗，但臺灣頭痛學會治療準則小組建議在特定、安全的情況下可以使用。

**臨床療效 (Clinical impression of effect)—0 (無效)：絕大多數患者不會改善；+ (可能有效)：少數患者臨床上有顯著改善；++ (有效)：部分患者臨床上有顯著改善；+++ (非常有效)：多數患者臨床上有顯著改善。

Differences Ergots vs. Triptans

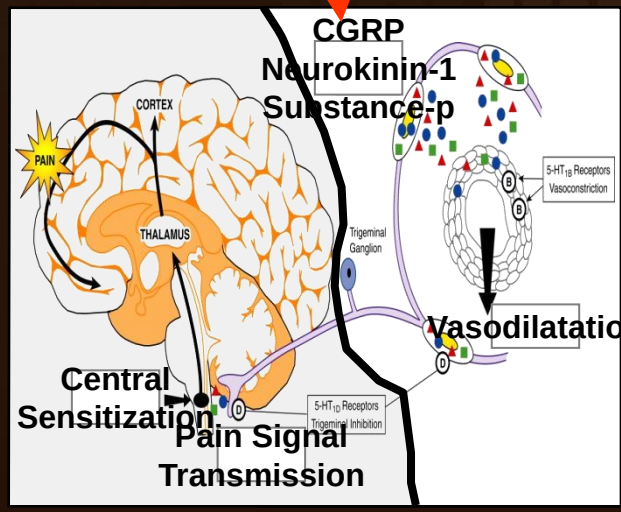
	Ergots	Triptans	
5-HT			
1A	++++	+	Dysphoria Nausea / Emesis
1B	+++	++	**Anti-migraine**
1D	+++	+++	**Anti-migraine**
2A	+++	–	Peripheral Vascular Effects Asthenia Dizziness
2C	+++	–	Peripheral Vascular Effects Asthenia Dizziness
Adrenergic			
α_1	+++	–	Peripheral Vascular Effects Asthenia Dizziness
α_2	+++	–	Peripheral Vascular Effects Asthenia Dizziness
Dopamine			
D_2	+++	–	GI / Nausea / Emesis

European guideline for acute Rx

- 1st-line: mild to moderate HA
  Acetaminophen, NSAID (including aspirin), opioid, combination of analgesics
- 1st-line severe HA
  Ergot and triptan (suma-, almo-, nara-, zolm-)
- Ergot (EFNS, Germany) (Recommend Level B)
- Ergot (Scotland) (Not recommend level A)
- Non-pharmacological therapy

Antonaci F. et al, J Headache Pain. 2010; 11:13-19

Promising drug in migraine Rx



- CGRP (calcitonin-gene related peptide) antagonist: **Block the CGRP receptors :**
  - **Inhibit the dilation of major cerebral vessels**
  - **Diminish neurogenic inflammation within the meninges**
  - **Can be used in CAD or Vascular disease**

Efficacy:

Telcapegpant 300 mg = zolmitriptan 5 mg > telcagepant 150 mg

The preventive treatment goals for the migraine sufferer

The goals for prophylaxis are as follows:

- Preventing or reducing the frequency, severity and duration of attacks.
- Improving the efficacy of acute abortive therapies.
- Improving the level of functioning and reducing disability from the disease.

Guidelines for migraine prevention

1. Recurrent migraine, significantly interfere with daily activities
2. Contraindication, fail of, or overuse of acute therapy (>10d/m)
3. Frequent headache with disability (≧4d /m) or ADE with acute therapies
4. Patient's preference
5. Uncommon migraine: hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction

(AAN/ EFNS guideline, 2000/ 2009)

(BASH Guideline, *2004)*

(Taiwan headache society, 2008)

The development and FDA approved for migraine preventive therapy

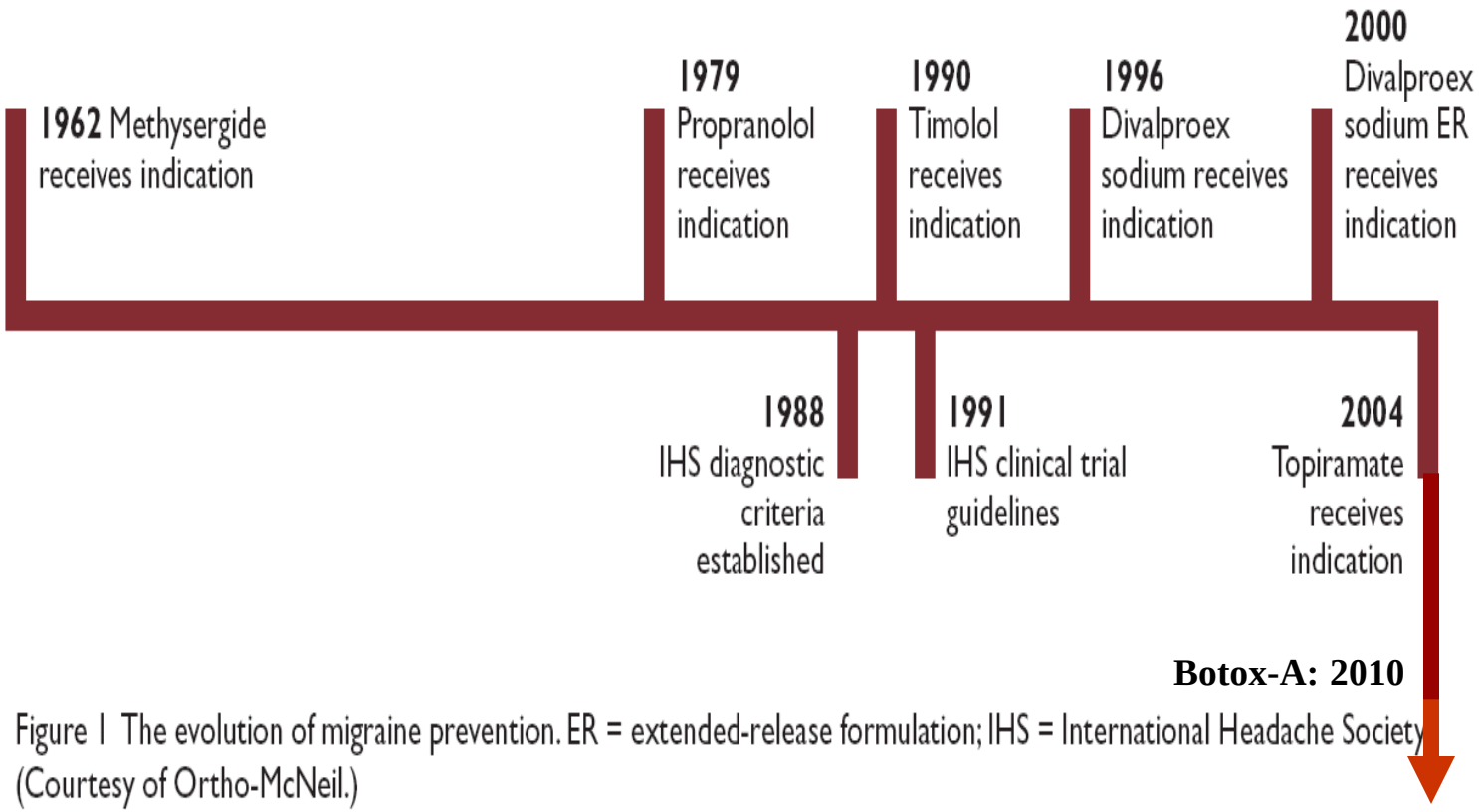


Figure 1 The evolution of migraine prevention. ER = extended-release formulation; IHS = International Headache Society. (Courtesy of Ortho-McNeil.)

e-based recommendations for ve treatment of migraine (US)

1. **Amitriptyline**
2. **Divalproex sodium**
3. **Propranolol/timolol**

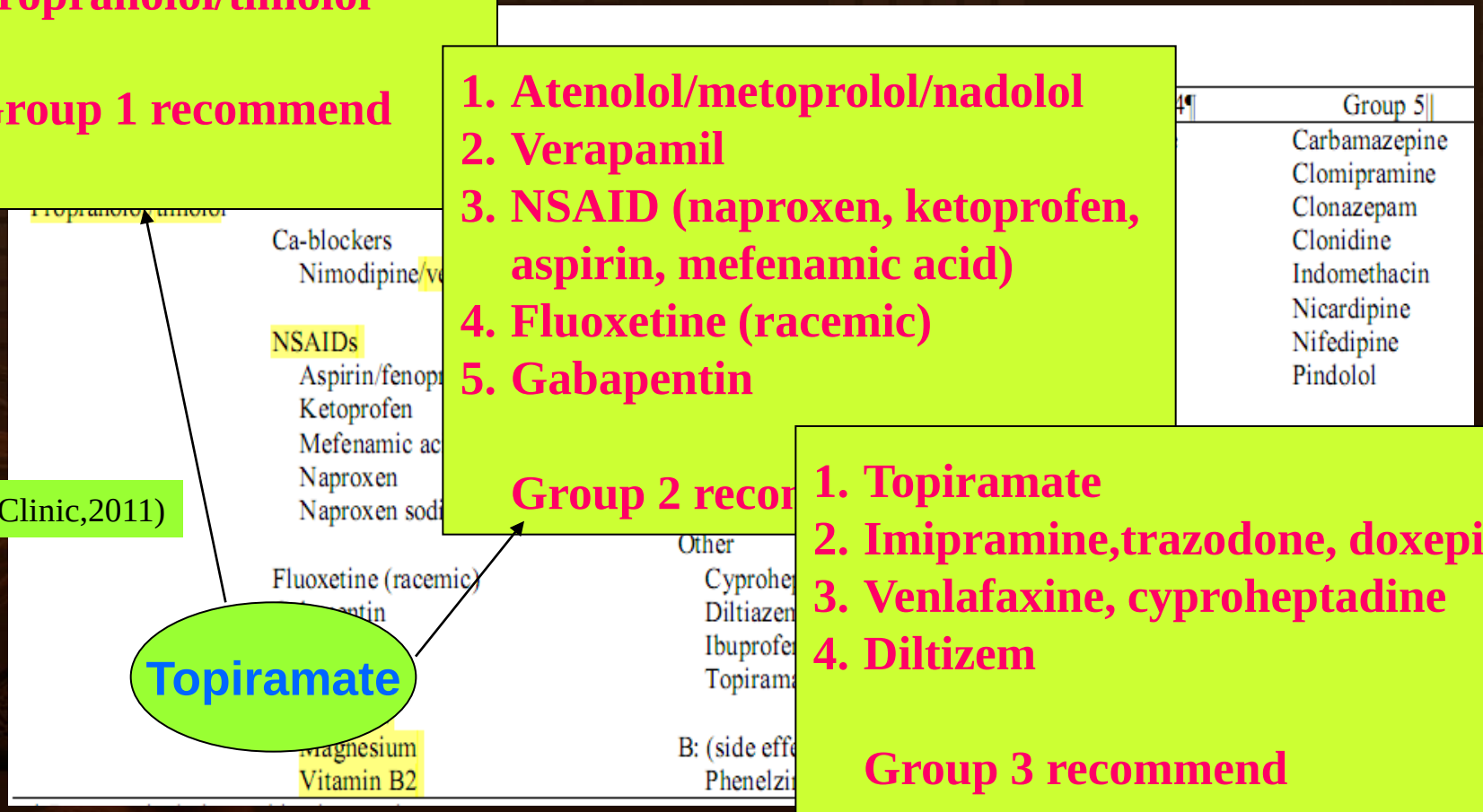
Group 1 recommend

1. **Atenolol/metoprolol/nadolol**
2. **Verapamil**
3. **NSAID (naproxen, ketoprofen, aspirin, mefenamic acid)**
4. **Fluoxetine (racemic)**
5. **Gabapentin**

Group 2 recor

1. **Topiramate**
2. **Imipramine,trazodone, doxepine**
3. **Venlafaxine, cyproheptadine**
4. **Diltizem**

Group 3 recommend



(MayoClinic,2011)

(AAN,2000)

Beta-blocker

Therapies	Quality of evidence*	Scientific effect*	Clinical impression of effect*	Adverse effects	Group*
Beta-blockers					
Atenolol	B	++	++	Infrequent to occasional	2
Metoprolol	B	++	+++	Infrequent to occasional	2
Nadolol	B	+	+++	Infrequent to occasional	2
Propranolol	A	++	+++	Infrequent to occasional	1
Timolol	A	+++	+	Infrequent to occasional	1

- In trials comparing ***amitriptyline*** and ***propranolol***, amitriptyline was significantly more efficacious in patients with mixed migraine and tension-type headaches, whereas propranolol was more effective in patients with migraine alone.
- Recommended dose of ***propranolol*** 20-160mg/d.
- Blockers with ISP-intrinsic sympatho-mimetic activity (acebutolol, alprenolol, oxprenolol, pindolol) seem to be ineffective for the prevention of migraine.

Calcium channel blocker

Therapies	Quality of evidence*	Scientific effect*	Clinical impression of effect*	Adverse effects	Group*
Calcium channel blockers					
Diltiazem	C	?	0	Infrequent to occasional	3a
Nimodipine	B	+	++	Infrequent to occasional	2
Verapamil	B	+	++	Infrequent to occasional	2

- Despite their widespread use as first-line agents and their perceived benefits based on anecdotal clinical experience, CCBs have not shown any solid experimental evidence to support their use in preventing episodic migraine headache.
- ***Flunarizine** is probably effective for preventive therapy and can be considered for the purpose.
- Recommended doses of ***flunarizine** 10mg/d.

(*Not available in US).

Antidepressants for migraine prophylaxis

Therapies	Quality of evidence*	Scientific effect*	Clinical impression of effect*	Adverse effects	Group*
Antidepressants					
Tricyclic antidepressants					
Amitriptyline	A	+++	+++	Frequent	1
Nortriptyline	C	?	+++	Frequent	3a
Protriptyline	C	?	++	Frequent	3a
Doxepin, imipramine	C	?	+	Frequent	3a
Selective serotonin reuptake inhibitors					
Fluoxetine	B	+	+	Occasional	2
Fluvoxamine, paroxetine, sertraline	C	?	+	Occasional	3a
Monoamine oxidase inhibitors					
Phenelzine	C	?	+++	Frequent	3b
Other antidepressants					
Bupropion, mirtazepine, trazodone venlafaxine	C	?	+	Occasional	3a

- Recommended doses of ***Amitriptyline*** *is* 10-100 mg/d.
- More effective in mixed migraine and TTH.

NSAIDs and other drugs for migraine prophylaxis

Therapies	Quality of evidence*	Scientific effect*	Clinical impression of effect*	Adverse effects	Group*
NSAIDs					
Aspirin	B			Infrequent	2
Fenoprofen					
Flurbiprofen					
Mefenamic acid					
Ibuprofen	C			Infrequent	3a
Ketoprofen	B			Infrequent	2
Naproxen/naproxen sodium	B			Infrequent	2
Serotonin antagonists					
Cyproheptadine	C	?	+	Frequent	3a
Methysergide	A	+++	+++	Frequent	4
Other					
Feverfew	B	++	+	Infrequent	2
Magnesium	B	+	+	Infrequent	2
Vitamin B2	B	+++	++	Infrequent	2

1. Methylsergide

Group (1=A) recommend in Europe, yet, ADE limited its use (retroperitoneal, or pulmonary fibrosis)

Alternative and complementary preventive therapies

B

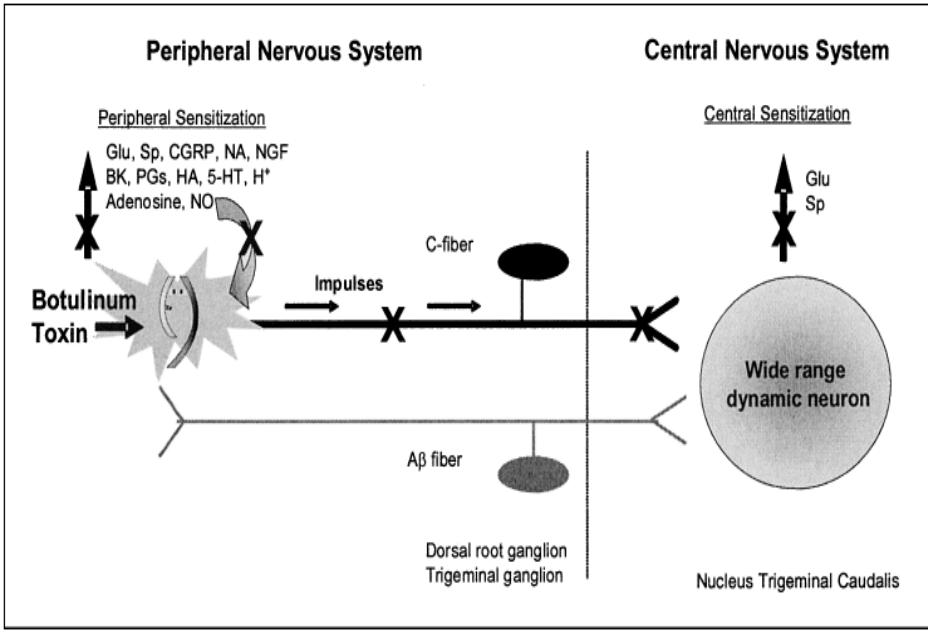
- Vitamin B2- 400mg/day (59% vs. 15% placebo)
- Magnesium-(regulate serotonin and NMDA receptor; GI upset)
- Coenzyme Q10-150~400mg/day (improved mitochondria dysfunction, expensive)

2

- Petasites hybridus (butterbur)-75mg bid. (inhibition of leukotriene synthesis, GI and liver dis.) (Neurology,2004)
- Feverfew (6.25mg tid for 4~12 wks)
- (Cephalalgia,2005)

BOTULINUM TOXIN
in the prevention of migraine

***(not approved by FDA)**



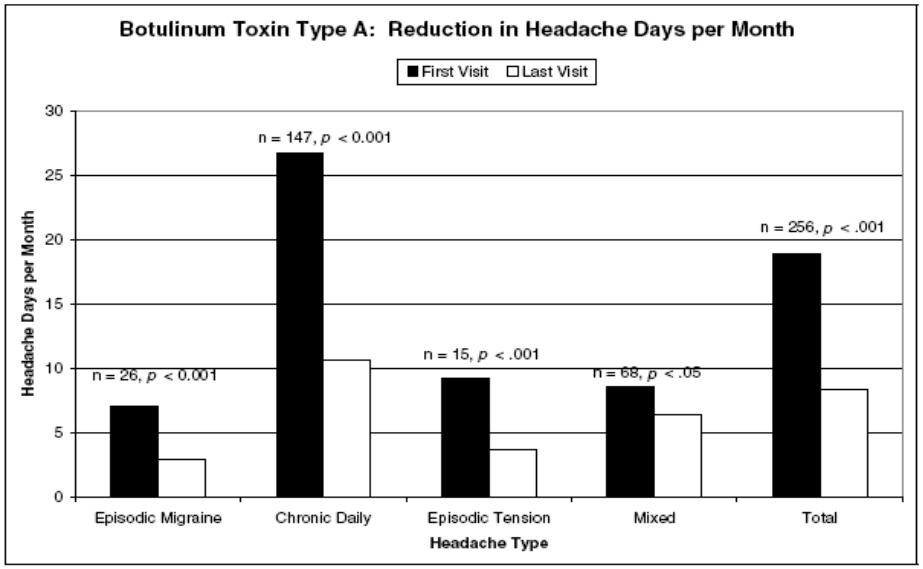
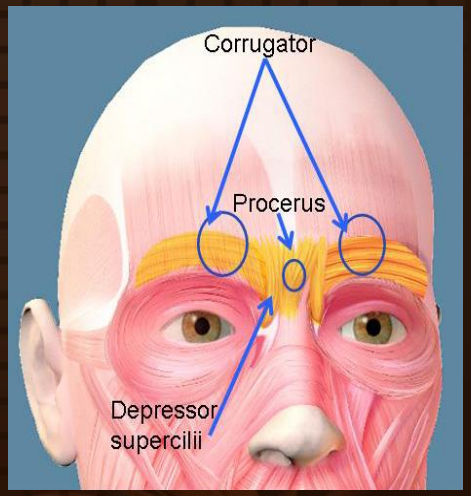
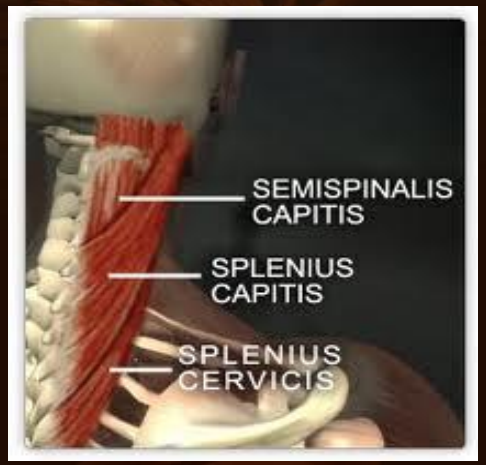


Fig 2.—Reduction in headache (HA) days per month with botulinum toxin type A treatment. Headache days decreased 56%, and HA frequency significantly declined, regardless of HA type (all, $P < .001$).

Silberstein, et al. Botulinum Toxin Type A as a Migraine Preventive Treatment. 2000; *Headache:* **40** (6), 445-450

Botox-A in chronic migraine





1. FDA-2010-10, only approved for chronic migraine (150u of standard dose at multi-sites)

2. 7-subtypes, only type A effective

3. Complicated mechanisms:
   = inhibit nociceptive inflammation and glutamate release
   = myo-relaxant effect
   = direct analgesic effect
   = inhibit central sensitization

Modern era of anticonvulsants for migraine prophylaxis

Therapies	Quality of evidence*	Scientific effect*	Clinical impression of effect*	Adverse effects	Group*
Antiepileptics					
Carbamazepine	B	++	0	Occasional to frequent	5
Divalproex sodium/sodium valproate	A	+++	+++	Occasional to frequent	1
Gabapentin	B	++	++	Occasional to frequent	2
Topiramate	C	?	++	Occasional to frequent	3a
	↓				↓
	Adult=B				2a

- ***Sodium valproate*** is recommended of 125-1000mg/d.
- ***Topiramate*** is recommended of 50-200 mg/d.
- ***Gabapentine*** is recommended 600-2400 mg/d.

(Wang SJ et al.)

Valproate

- **Divalproex sodium (Depakote) was approved for migraine prophylaxis by the FDA in 1996, the clinical efficacy dose 500~1500mg**
- **Nausea , asthenia, somnolence, weight gain, hair loss, tremor and teratogenic potentials of ADE**
- **Recommended for patient with prolonged or atypical migraine aura, not in patients with liver disease**

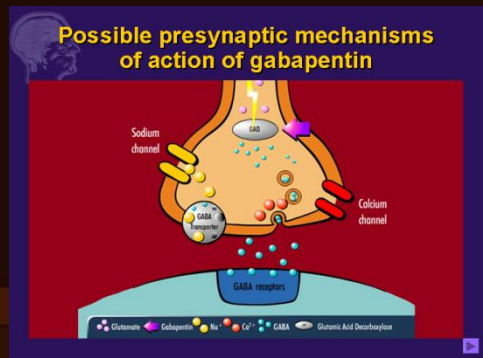
Drug [dosage (mg/day)]	Study design	No. of patients (type of migraine)	Treatment duration (wk; adjustment + maintenance)	Main outcome
Valproate [800]	Crossover	29 (MA, MO)	8	Mean attacks (4wk): valproate 4.4 ($p < 0.001$); placebo 7.8
Valproate [1000, 1500][a]	Crossover	34 (MO)	12	Mean days with migraine (4wk): valproate 3.5 ($p = 0.002$); placebo 6.1
Divalproex sodium [mean 1087][b]	Parallel groups	107 (MA, MO)	4 + 8	Mean attacks (4wk): divalproex sodium 3.5 ($p < 0.001$); placebo 5.7
Divalproex sodium [500, 1000, 1500]	Parallel groups	176 (MA, MO)	4 + 8	Mean reduction in attacks (4wk): divalproex sodium 1.7-2.0[c] ($p \leq 0.05$); placebo 0.5

CNS Drugs 2002; 16 (9)

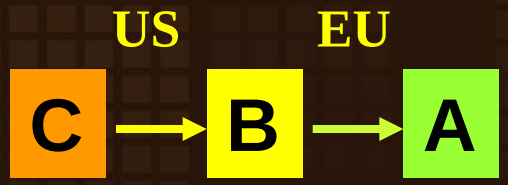
Gabapentin

- Gabapentin was introduced as an AED in the US in 1994. It has now been widely used in migraine prevention, in the treatment of neuropathic pain, and in many other disorders in addition to epilepsy.
- Starting dose 300mg once a day, increase to 600-2400mg/day in divided dose three times a day for preventive therapy. ADE (drowsiness, dizzy).
- It should be used for reservation in cases who are difficult to manage with current available strategies since it has a reasonable tolerability and safety profile. (by authors' opinions in Cochrane review)

B



Topiramate



- Topiramate is the newest FDA-approved neurostabilizer medication indicated for the prevention of migraine.
- Pooled ADE: paresthesia (35-51%), fatigue(14-19%), loss of appetite (9-15%), nausea, abdominal pain, diarrhea(9-14%); sleep disturbance and cognitive problems (6%) and weight loss.
- Rarely for kidney stones, acute angle-closure glaucoma, acute myopia.
- Metabolic acidosis, suicide thought, birth defect in pregnancy (in 2008)

Others (1)

- **Pizotifen*** (26 trials): inconsistent evidence, although effective, but poor tolerated ADE with higher withdraw rate.
  (effective doses 1.5-6mg/d).

A 4

- **Lisuride*** (6 trials): consistent benefits and less ADE.
  (effective doses 0.075-0.15mg/d).

A 1

- **Methylsergide**: effective but poor tolerated ADE.
  (doses 6mg/d). (ADE: retroperitoneal fibrosis)
  Used for 6 months, should be withdraw for 4-5 wks.

A 4

- **Estradiol**: some benefits in female with MC, not for men or female without MC. (effective doses 1.5mg/ d)
  Combined estrogen + progesterone had no solid benefits.

B 2

(*not in US)

Others (2)

- Dihydro-ergotamine (DHE*): 10 mg/d. (not available in US).
- Cafergot compounds (ergot with caffeine): insufficient evidence in prevention.
- ACEI (lisinopril), ARB (candesartan): can be 2nd or 3rd line of preventive therapy (Ann Pharmocother, 2010)
- Corticosteriods: for rescue use in status migrainous, not for prevention.
- Opioids: not for preventive strategy.
- Lamotrigine, Clonazepam, Carbamazepine: not effective.

Potential mechanisms of migraine preventive agents

- Migraine and epilepsy share several clinical features and respond to many of the same pharmacological agents, suggesting that similar mechanism may be involved in their pathophysiology.

	Glutamate	GABA	Norepinephrine	Serotonin	Ion Channel Alterations
Beta blockers	↓	–	↓↓↓	–	+++
TCAs	↓	↑	↑	↑↑↑	++
CCAs	↓↓	–	–	–	++
Valproate	↓↓↓	↑↑↑	–	–	++
Gabapentin	–	↑↑	–	–	++
Topiramate	↓↓↓	↑↑↑	–	–	+++

(Adapted from Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache and Other Head Pain.* Oxford University Press; 2001.)

Dose and titration of drug therapy for migraine

	Dose Range	Onset of Action	Need to Titrate
Tricyclic antidepressants*	25–150 mg/day	4–6 weeks	Yes
Beta blockers†	60–320 mg/day	4–6 weeks	Yes
Calcium-channel blockers‡	240–320 mg/day	4–6 weeks	Yes
Valproic acid	500–3,000 mg/day	4–6 weeks	Yes
Gabapentin	1,800–2,400 mg/day	4–6 weeks	Yes
Topiramate	100–200 mg/day	4–6 weeks	Yes

* Amitriptyline and nortriptyline.
† Propranolol.
‡ Verapamil.

(James W. Banks, CEC, 2004)

MIPCA guidelines for the migraine prophylaxis (2004)

Recommended prophylactic medications:

First line medication: ***(start at low dose, and escalated if necessary)***

- Beta-blockers (propranolol, metoprolol, timolol or nadolol).
- Anticonvulsants, such as sodium valproate*.
- Antidepressants, such as amitriptyline*.

Second line medication:

- Serotonin and histamine antagonists (pizotifen, methysergide, cyproheptadine)

Alternative therapies:

- Some complementary medications, including feverfew, magnesium, vitaminB2, acupuncture and butterbur may be used *in addition to* (not instead of) the patient's existing acute and/or prophylactic therapies.

(Migraine in primary care advisors, Jan 2004)

Table 2: Guide to choosing migraine prophylactic drugs

First-line agents	Second-line agents	Third-line agents
Amitriptyline	Topiramate	Flunarizine
Propranolol	Gabapentin	Pizotifen
Nadolol	Venlafaxine	Divalproex sodium
	Candesartan	
	Lisinopril	
	Magnesium	
	Butterbur	
	Coenzyme Q10	
	Riboflavin	

CANADA GUIDELINE (CMAJ, 2010)

Hypertension or cardiovascular disease	Propranolol, nadolol, lisinopril, candesartan
Initial insomnia	Amitriptyline
Mood disorder	Amitriptyline, venlafaxine
Seizure disorder	Topiramate, divalproex sodium, gabapentin
Pregnant or trying to conceive	Magnesium
Obese	Topiramate
Poor tolerance of medication side effects	Riboflavin, coenzyme Q10, butterbur, propranolol, lisinopril, candesartan

Drugs used in France for migraine prophylaxis in adult

Propranolol
Metoprolol
Oxetorone
Amitriptyline

1st line recommen

Pizotifen
Flunarizine
Valproate sodium
Topiramate

2nd line recommend

		Adverse Effects	Contraindications
		Common: asthenia, poor exercise tolerance; rare (<1% of attacks): insomnia, nightmares, impotence, depression, hypoglycemia	Asthma, heart failure, atrioventricular block, bradycardia (note: possible aggravation of migraine with aura)
	3 tablets)	Common: somnolence; rare (<1% of attacks): diarrhea requiring discontinuation	–
		ight gain	Glaucoma, prostatic adenoma
		ain; rare (<1% of vertigo, muscle	Glaucoma, urethroprostatic disorders
	(0.5–1.5		
Valproate sodium†	500–10(	ence, tremor; ion test results	Liver disease
Methysergide maleate	2–6 mg disconti for 1 mo	somnia; rare neal fibrosis	Hypertension, coronary insufficiency, arteriopathy, gastric ulcer; liver and/or kidney failure
Flunarizine HCl	10 mg (evening) consecu	nt gain; rare extrapyramidal	Depression, extrapyramidal syndrome
Gabapentin†	1200–24	somnolence,	Hypersensitivity to gabapentin
Indoramin	50 mg	Somnolence, nasal congestion, dry mouth, ejaculation disorders	Hypersensitivity to one of the active compounds; Parkinson's disease; severe heart, liver, and/or kidney failure
Topiramate	50–200 mg	Vertigo, ataxia, somnolence, dysarthria, paresthesia, irritability, asthenia, weight loss	Hypersensitivity to one of the active compounds and/or to sulfamides

HCl = hydrochloride.
*All of these drugs are given in tablet form.
†This drug has not been approved for the prophylaxis of migraine.

(French Guideline, 2004)

Table 4 Recommended substances (drugs of first choice) for the prophylactic drug treatment of migraine

Substances	Daily dose (mg)	Level
Betablockers		
Metoprolol		A
Propranolol		A
Calcium channel blocke		
Flunarizine		A
Antiepileptic drugs		
Valproic acid		A
Topiramate	25–100	A

AEDs
Beta-blockers
CCBs

Table 5 Drugs of second choice for migraine prophylaxis (evidence of efficacy, but less effective or more side effects than drugs of Table 6)

Substances	Daily dose (mg)	Level
Amitriptyline	50–150	B
Venlafaxine	75–150	B
Naproxen	2 × 250–500	B
Petasites	2 × 75	B
Bisoprolol	5–10	B

Table 6 Drugs of third choice for migraine prophylaxis (only probable efficacy)

Substances	Daily dose	Level
Acetylsalicylic acid	300 mg	C
Gabapentin	1200–1600 mg	C
Magnesium	24 mmol	C
Tanacetum parthenium	3 × 6.25 mg	C
Riboflavin	400 mg	C
Coenzyme Q10	300 mg	C
Candesartan	16 mg	C
Lisinopril	20 mg	
Methysergide	4–12 mg	

(EFNS, 2009)

Co-morbidity of migraine

Table 4 **Therapeutic Opportunities and Limitations in Migraine Prevention**

Condition	Consider	Avoid
Depression	TCA	Beta blocker
Anxiety	TCA, beta blocker	
Sleep disturbance	TCA	
Overweight/obese	Topiramate	TCA, gabapentin, valproate
Bipolar disorder	Valproate, topiramate	TCA
Epilepsy	Topiramate, valproate	TCA
Raynaud's phenomenon	Calcium-channel blocker	Beta blocker, ergot

TCA = tricyclic antidepressant.

Migraine in Children: Overview of Pediatric Migraine

***In children,** attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

(Child Neurology Society, 2004)

1-48 hours
Bilateral
Autonomic disturbance
Obvious postdrome s/s

Management of the child and adolescents with migraine headache

Effectively
with Flunarizine (not in US)
and Propranolol

(Cochrane review,2008)

Non-pharmacological management
*Acetaminophen
*NSAID
*Amitriptyline
*SSRI
*Pizotifen
*Topiramate
*Valproate sodium

*suggest but not recommend

		n	Efficacy	Adverse effects
				Occasional to frequent
		42	76% had >50% reduction headache frequency	
		10	$p = 0$	
		75	$p < 0.001$	Occasional to frequent
		19	$p < 0.0001$	Occasional to frequent
Tricyclic antidepressants amitriptyline				
1 mg/kg (9–15 y)				
10 mg (3–12 y)				
Antihistamines				
Cyproheptadine 4 mg (3–12 y)				
Calcium channel blockers				
Flunarizine 5 mg (5–11 y)				
5 mg (10–13 y)				
Nimodipine 10–20 mg (7–18 y)				
Antihypertensive agents				
Propranolol				
80 mg (3–12 y)				
6–120 mg (7–16 y)				
3 mg/kg/d (6–12 y)				
Clonidine				
0.07–0.1 mg (7–14 y)	II	43	NS	Occasional to frequent
0.025–0.05 mg (≤15 y)	II	57	32%: 34%—NS	

(Child neurology society, 2004)

Migraine during pregnancy

- The greatest frequency of migraine attacks occurs during the first trimester, and this is when the fetus is also at the greatest risks from aborticfacient and teratogenic drugs.
- Prophylactic agents for migraine therapies should be avoided during pregnancy, including all ergot alkaloids.
- In exceptional circumstances or during second and third trimesters, some medication can be used. Prozac (B), inderal, amitriptyline, gabapentin, and topiramate (C), NSAID (C).
- **Deparkine, B2, ACEI, ARB--(X)**

Therapy	Category[a]
Short-term	
Aspirin (acetylsalicylic acid)	Unlabelled
Paracetamol (acetaminophen)	Unlabelled
Dihydroergotamine	X
Ergotamine	X
Isometheptene	Unlabelled
Metoclopramide[d]	B
Naproxen	B[b]
NSAIDs[c]	B or C[b]
Opioids	C
Prochlorperazine[d]	C
Serotonin 5-$HT_{1B/1D}$ receptor agonists	C
Prophylactic	
Valproate semisodium	D
Flunarizine	Unlabelled
Fluoxetine[d]	C
Methysergide	X
Pizotifen	Unlabelled
Propranolol	C
Timolol	C
Topiramate[d]	C
TCAs[d]	C
Valproic acid (sodium valproate)	D
Herbal products	Unlabelled

(AFPP, 2006)

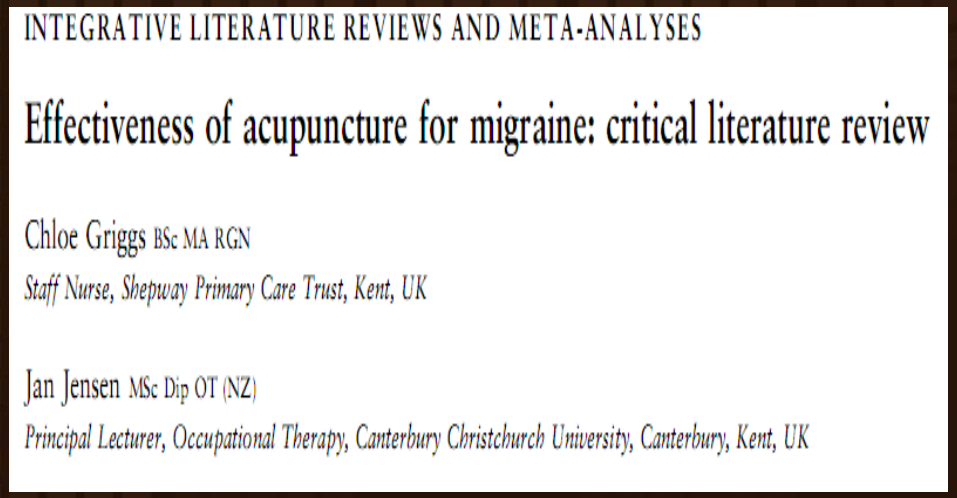
US guideline for migraine

- National Headache Foundation (2004):
  - 1st line=> amitriptyline(10-150mg),divalproex(125-200mg), timolol (blocadren:10-30mg), propranolol (20-160mg), topiramate (50-150mg)

  - Alternative therapy=> acupuncture with CBT, biofeedback, relaxation

- AAN (2009):
  Not endorsed for hypnosis, acupuncture, TENS, cervical manipulation, occlusal adjustment, HBO

Acupuncture in migraine-updating evidence



INTEGRATIVE LITERATURE REVIEWS AND META-ANALYSES

Effectiveness of acupuncture for migraine: critical literature review

Chloe Griggs BSc MA RGN
Staff Nurse, Shepway Primary Care Trust, Kent, UK

Jan Jensen MSc Dip OT (NZ)
Principal Lecturer, Occupational Therapy, Canterbury Christchurch University, Canterbury, Kent, UK

1. **Trials of acupuncture for migraine have produced conflicting results**

2. **The benefits of acupuncture for migraine prevention in Cochrane Review: Recommend A**

(AAFP, 2010)

Pacific University
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School of Physician Assistant Studies — Theses, Dissertations and Capstone Project

1-1-2011

Acupuncture for Treatment of Acute Migraine: A Systematic Review

Virginia R. Whitney
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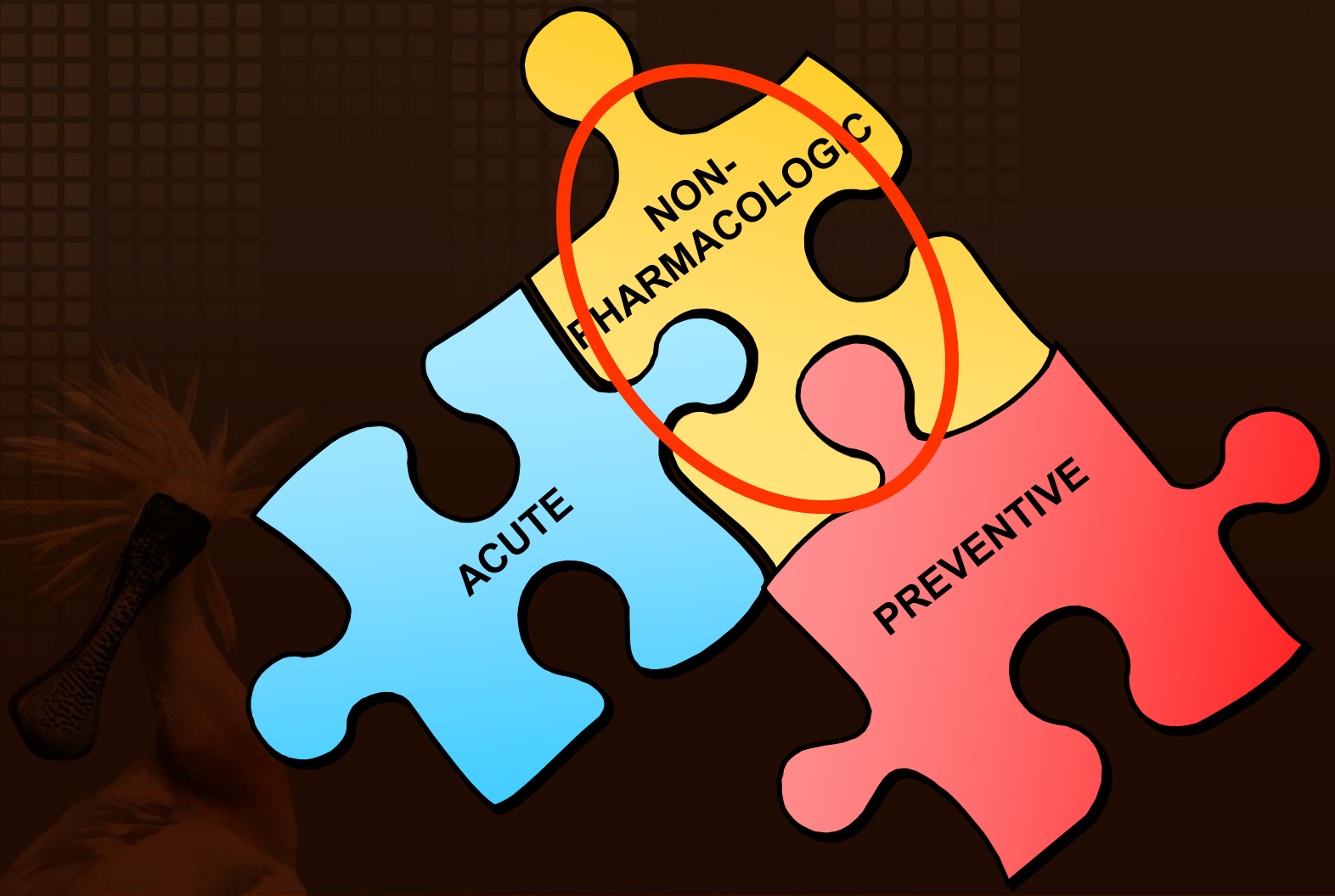
(2011)

Beyond the pharmacological treatment



Evidenced-Based Guidelines For Migraine Headache: Behavioral and Physical Treatments

Table 1: Behavioral Treatment Migraine Efficacy Summary

Intervention	No Studies in analysis	Mean weighted % improvement (range)	Effect size (95% confidence interval)*
I. Studies included in effect size analysis			
"No treatment" (control)	12	5 (-20 - 19)	0
Placebo	4	9 (-7 - 37)	0.16 (-0.31-0.63)
Relaxation	5	41 (6.2-78)	0.55 (0.14-0.96)
Thermal biofeedback	3	30 (13-60)	0.38 (-0.18-0.94)
Thermal biofeedback + relaxation	8	33 (21-52)	0.40 (0.01-0.79)
EMG biofeedback	3	51 (36-58)	0.77 (0.24-1.3)
Cognitive-behavioral therapy	5	39 (29-51)	0.54 (0.13-0.94)
Cognitive-behavioral therapy + biofeedback	5	38 (21-46)	0.37 (-0.23-0.97)

(2000, AAN)

Summary

- 治療可分non-pharmacologic, acute and preventive三方面。
- 急性治療最佳化強調分層治療、早期投藥與避免過度使用急性治療。
- 輕中度偏頭痛先選擇口服NSAIDs，替代藥物包括aspirin、複方 止痛藥、靜脈/肌肉注射NSAIDs或麥角胺。
- 中重度偏頭痛，建議口服翠普登或是麥角胺，宜在頭痛早期使用，但也不宜在aura給藥。
- 預防藥物主要先為B-blocker, Amitriptyline, Divalproate,及Topiramate; 其次為SSRI, CCB, Gabapentin, Rivoflavin, and NSAID.
- 衛教、病人日記仍然相當重要。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Thank you for attention