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秋季頭痛讀書會
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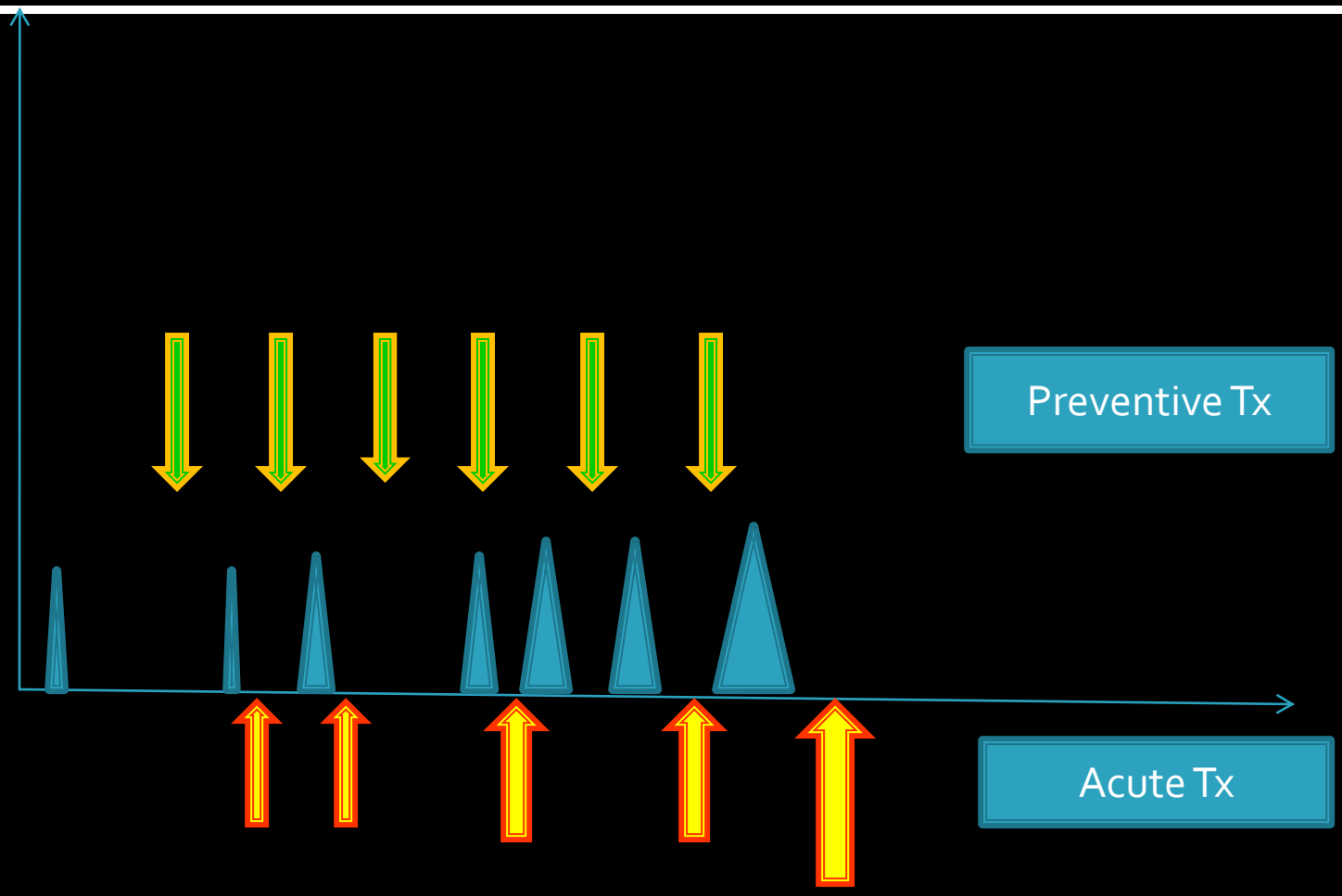
NSAIDs for Migraine: a Sword with Double Blades

Chronic migraine
Acute & Preventive Tx



Part 1 NSAIDs for Migraine

- Acute (Abortive) Tx
- Preventive (Prophylaxis) Tx ??
- Medication overuse headache?

美、歐、英

Acute vs Preventive Treatment

Medicine Cabinet

Migraine prophylaxis in adult patients

Summary points

- Not all patients are candidates for prophylactic therapy for migraine; physicians must evaluate whether prophylaxis is indicated in a patient
- Prophylaxis of migraines is not a cure; abortive measures will still be necessary in most patients
- A headache diary is essential to identify and avoid triggers and to evaluate therapy
- For prophylactic drug therapy, choose the agent that has the potential for the highest benefit and lowest risk to the patient
- Although their efficacy is questionable, alternative therapies may have some role in migraine prophylaxis

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Competing interests:
None declared

West J Med
2000;173:341-345

Special Article

Neurology 2000;55:754–763

Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Stephen D. Silberstein, MD, FACP, for the US Headache Consortium*

Table 1 *Evidence summary for treatment of acute attacks of migraine*

Drug	Quality of evidence*	Scientific effect*	Clinical impression of effect*	Adverse effects	Role (by consensus)
Triptans (serotonin$_{1B/1D}$ receptor agonists)					
Sumatriptan nasal spray	A	+++	+++	Occasional	Moderate-to-severe migraine. Useful when nonoral route needed. Less severe migraine when nonopiate medications fail.
Oral triptans					Moderate-to-severe migraine. Less severe migraine when nonopiate medications fail.
Naratriptan	A	++	++	Infrequent	
Rizatriptan	A	+++	+++	Occasional	
Sumatriptan	A	+++	+++	Occasional	
Zolmitriptan	A	+++	+++	Occasional	
Sumatriptan SC	A	+++	+++	Frequent	Moderate-to-severe migraine. Useful when nonoral route needed. Less severe migraine when nonopiate medications fail.
Ergot alkaloids and derivatives					
DHE IV	B	++	+++	Frequent	Low recurrence.
DHE SC/IM	B	+++/++	+++	Occasional	Moderate-to-severe migraine. Less severe migraine when nonopiate medications fail.
DHE IV plus antiemetics	B	+++	+++	Frequent	Status migrainosus. Therapy of choice in emergency department.
DHE nasal spray	A	++	++	Occasional	Moderate-to-severe migraine. Less severe migraine when nonopiate medications fail.
					Low recurrence.
Ergotamine	B	+	++	Frequent	Consider for selected patients with moderate-to-severe migraine.
Ergotamine plus caffeine					
Antiemetics					
Chlorpromazine IM/IV	C/B	++	++	Mild to moderate	Adjunct therapy. May be choice for acute therapy.
Metoclopramide IM	B	+	+	Infrequent to occasional	Adjunct therapy. May be choice for acute therapy.
PR/IV	B	++	?/++		
Prochlorperazine PR/IM	B	+++	+/++	Occasional	IM/IV adjunct first-line therapy in emergency department or office; consider PR as adjunct.
IV	B	+++	+++	Frequent	
NSAIDs and nonopiate analgesics					
Acetaminophen	B	0	+	Infrequent	Pregnant migraineur.
Ketorolac IM	B	+	++	Infrequent	Consider in emergency department.
Oral NSAIDS				Occasional	First-line for mild-to-moderate migraine.
Aspirin	A	++	++		
Diclofenac K	B	++	++		
Flurbiprofen	B	+	++		
Ibuprofen	A	++	++		
Naproxen	B	+	++		
Naproxen sodium	A	++	++		
Combination analgesics					
Acetaminophen, aspirin, caffeine	A	+++	++	Infrequent	First-line for migraine.

Table 3 *Preventive therapies for migraine*

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
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
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
Calcium channel blockers					
Diltiazem	C	?	0	Infrequent to occasional	3a
Nimodipine	B	+	++	Infrequent to occasional	2
Verapamil	B	+	++	Infrequent to occasional	2
NSAIDs					
Aspirin	B	+	+	Infrequent	2
Fenoprofen					
Flurbiprofen					
Mefenamic acid					
Ibuprofen	C	?	+	Infrequent	3a
Ketoprofen	B	+	+	Infrequent	2
Naproxen/naproxen sodium	B	+	+	Infrequent	2

Headache

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2012.02185.x
Published by Wiley Periodicals, Inc.

Research Submissions

The 2012 AHS/AAN Guidelines for Prevention of Episodic Migraine: A Summary and Comparison With Other Recent Clinical Practice Guidelines

Elizabeth Loder, MD, MPH; Rebecca Burch, MD; Paul Rizzoli, MD

(*Headache* 2012;52:930-945)

Table 1.—AHS/AAN Migraine Prevention Guidelines
Drugs Recommended for Use

Drug	Examples of Studied Doses
Level A: established as effective	
Should be offered to patients requiring migraine prophylaxis	
Divalproex/sodium valproate	400-1000 mg/day
Metoprolol	47.5-200 mg/day
Petasites (butterbur)	50-75 mg bid
Propranolol	120-240 mg/day
Timolol	10-15 mg bid
Topiramate	25-200 mg/day
Level B: probably effective	
Should be considered for patients requiring migraine prophylaxis	
Amitriptyline	25-150 mg/day
Fenoprofen	200-600 mg tid
Feverfew	50-300 mg bid; 2.08-18.75 mg tid for MIG-99 preparation
Histamine	1-10 ng subcutaneously twice a week
Ibuprofen	200 mg bid
Ketoprofen	50 mg tid
Magnesium	600 mg trigmagnesium dicitrate qd
Naproxen/naproxen sodium	500-1100 mg/day for naproxen 550 mg bid for naproxen sodium
Riboflavin	400 mg/day
Venlafaxine	150 mg extended release/day
Atenolol	100 mg/day
Level C: possibly effective	
May be considered for patients requiring migraine prophylaxis	
Candesartan	16 mg/day
Carbamazepine	600 mg/day
Clonidine	0.75-0.15 mg/day; patch formulations also studied
Guanfacine	0.5-1 mg/day
Lisinopril	10-20 mg/day
Nebivolol	5 mg/day
Pindolol	10 mg/day
Flurbiprofen	200 mg/day
Mefenamic acid	500 mg tid
Coenzyme Q10	100 mg tid
Cyproheptadine	4 mg/day

European Journal of Neurology 2006, **13:** 560–572 doi:10.1111/j.1468-1331.2006.01411.x

EFNS TASK FORCE ARTICLE

EFNS guideline on the drug treatment of migraine – report of an EFNS task force

Members of the task force: S. Evers[a], J. Áfra[b], A. Frese[a], P. J. Goadsby[c], M. Linde[d], A. May[e] and P. S. Sándor[f]

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Acute Tx_EFNS

Substance	Dose	Level of recommendation	Comment
Acetylsalicylic acid (ASA)	1000 mg (oral)	A	Gastrointestinal side effects, risk of bleeding
	1000 mg (i.v.)	A	
Ibuprofen	200–800 mg	A	Side effects as for ASA
Naproxen	500–1000 mg	A	Side effects as for ASA
Diclofenac	50–100 mg	A	Including diclofenac-K
Paracetamol	1000 mg (oral)	A	Caution in liver and kidney failure
	1000 mg (supp.)	A	
ASA plus, paracetamol plus and caffeine	250 mg (oral), 200–250 mg and 50 mg	A	As for ASA and paracetamol
Metamizol	1000 mg (oral)	B	Risk of agranulocytosis
	1000 mg (i.v.)	B	Risk of hypotension
Phenazon	1000 mg (oral)	B	See paracetamol
Tolfenamic acid	200 mg (oral)	B	Side effects as for ASA

European Journal of Neurology 2006, **13:** 560–572
EFNS TASK FORCE ARTICLE

Preventive Tx_EFNS

Table 6 Recommended substances (drugs of first choice) for the prophylactic drug treatment of migraine

Substances	Daily dose	Level
Betablockers		
Metoprolol	50–200 mg	A
Propranolol	40–240 mg	A
Calcium channel blockers		
Flunarizine	5–10 mg	A
Antiepileptic drugs		
Valproic acid	500–1800 mg	A
Topiramate	25–100 mg	A

Table 7 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
Naproxen	2 × 250–500	B
Petasites	2 × 75	B
Bisoprolol	5–10	B

European Journal of Neurology 2006, **13:** 560–572
EFNS TASK FORCE ARTICLE

NSAIDs

In some comparative trials, ASA was equivalent to or worse than a comparator (which had shown efficacy in other trials) but never has achieved a better efficacy than placebo in direct comparison. However, in two large cohort trials, ASA 200–300 mg reduced the frequency of migraine attacks [110,111]. Naproxen 1000 mg was better than placebo in three controlled trials [112–114]. Moreover, tolfenamic acid showed efficacy in two placebo-controlled trials [115,116]. Other NSAIDs studied were ketoprofen, mefenamic acid, indobufen, flurbiprofen, and rofecoxib [117]. However, all studies for the later substances were small and had no sufficient design.

Reasonable for Menstrual Migraine

Specific situations

Menstrual migraine

In the recent second edition of IHS diagnostic criteria, the entity of menstrual migraine is to be found in the appendix (and not the main criteria), reflecting a certain degree of uncertainty about the best criteria. Nevertheless, different drug regimes have been studied to treat this condition of quite some importance in clinical practice. On the one hand, acute migraine treatment with triptans has been studied showing the same efficacy of triptans in menstrual migraine attacks as compared with non-menstrual migraine attacks. On the other hand, short-term prophylaxis of menstrual migraine has been studied.

Naproxen sodium (550 mg twice daily) has been shown to reduce pain including headache in the premenstrual syndrome [151]. Its specific effects on men-

British Association for the Study of Headache

Concise Headache Management Guidelines

For further details and references readers are referred to the full published Guidelines (available at on this website). Drug information sheets can be found at www.headache.exeter.nhs.uk

Analgesics

- Most will have tried Paracetamol, Aspirin and Ibuprofen
- Prescription NSAID's (Naproxen, Diclofenac)
- Anti-emetics (Domperidone)
- Then:- **Triptans** Differences can be utilised in practice

	Trade name	Tablets	Melt	Nasal	Subcutaneous
Sumatriptan	Imigran	£4.95-£8		£6	£22.60
Zolmitriptan	Zomig	£4	£4	£6.75	
Naratriptan	Naramig	£4			
Rizatriptan	Maxalt	£4.46	£4.46		
Eletriptan	Relpax	£3.75			
Almotriptan	Almogran	£3.25			
Frovatriptan	Migard	£2.95			

Migraine - Preventive Treatment

Try adequate doses for about 6 months

First choice	•Betablockers (Propranolol, Atenolol)
Second choice	•Antiepileptic drugs (Valproate, Topiramate) Except in young women
Third choice	•Antidepressants (Amitriptyline, Nortriptyline)
Fourth choice	•Serotonin antagonists (Pizotifen, Methysergide)
Fifth choice	•Riboflavin, coenzyme Q10, magnesium
Special cases	•Menstrual migraine: NSAIDs, continuous contraceptive pill, naratriptan, frovatriptan •Exercise induced: betablockers, indomethacin

偏頭痛預防性藥物治療準則

台灣頭痛學會治療準則小組

表．偏頭痛的預防性治療藥物

藥物種類（有效劑量 mg/d）	在偏頭痛預防性治療中的注意事項	*證據強度	+臨床療效	^統計測量	%推薦等級
乙型阻斷劑 beta- blocker	~ 用於偏頭痛預防優先選擇藥物，但氣喘、心				
propranolol (20-160)	臟傳導阻滯、糖尿病、末梢血管疾病、憂鬱	A	+++	+++	I
atenolol (50-100)	症患者應避免使用 acebutolol，pindolol 等	B	++	++	II
metoprolol (50-200)	有 intrinsic sympathomimetic activity (ISA)	B	++	+++	II
nadolol (40-80)	之 beta blockers 預防偏頭痛無效.	B	+	+++	II
	~ 一次或分次服用。				
抗憂鬱劑 anti-depressants					
amitriptyline (10-75mg)	~ amitriptyline 為優先選擇，其餘療效變異大，劑量不如治療憂鬱症之高。青光眼、攝護腺患者禁用。需小心嗜睡、無力副作用。睡前或分次。	A	+++	+++	I
fluoxetine (10-40mg)	~ 無法用 amitriptyline 時考慮此藥。	B	+	+	II
paroxetine, sertraline (?)	~ fluoxetine 無法使用時之替代藥。	C	+	?	III
venlafaxine (75-150mg)	~ SNRI 抗憂鬱劑用於預防偏頭痛療效尚未證實。	B	++	?	II
duloxetine (30-90mg)		C	+	?	III
抗癲癇藥物 anti-epileptic drug					
sodium valproate ER (500)	~ 預防偏頭痛須從低劑量（250mg）起始，	A	+++	+++	I
divalproex sodium (500-1000)	ER 長效型一天一次睡前，一般型則需分次。	A	+++	+++	I
valproic acid (300-1800)	注意肝臟代謝，副作用水腫、肥胖。				
topiramax (50-100)	~ topiramate 注意肢端麻木、認知障礙。	A	+++	+++	I
gabapentin (600-1800)	~ gabapentin 小心嗜睡、頭暈、不穩。	B	++	++	II
(vigabatrin, cabamazapine,	~ 此四類藥物，用於預防偏頭痛療效不明，	B	?	?	V
lamotrigine, clonazepam)	不建議使用。				
鈣離子阻斷劑 calcium channel blocker					
flunarizine (5-10)	~ flunarizine 在歐洲為優先建議偏頭痛預防	A	+++	+++	I
nimodipine (60-120)	用藥（>12 歲）。老年人須注意錐體外副作用。	B	+	+	II
verapamil (120-240)		B	+	+	II
diltiazem (?)		C	0	?	III

偏頭痛預防性藥物治療準則

台灣頭痛學會治療準則小組

表.（續）偏頭痛的預防性治療藥物

藥物種類（有效劑量_mg/d）	在偏頭痛預防性治療中的注意事項	*證據強度	+臨床療效	^統計測量	%推薦等級
非類固醇類抗發炎製劑 NSAIDs	~ NSAID 預防偏頭痛須注意腸胃道副作用，長期				
ketorprofen (150)	使用者需注意肝腎功能，劑量最好從最低開始。	B	+~++	+~++	II
aspirin (1300)	臨床上依個人情形使用（單一使用時需較高劑				
fenoprofen (600-1800)	量，在合併療法時可減半開始，或更低劑量）。				
mefenamic acid (1500)	合併療法發揮療效時，應先停止 NSAID，以其				
naproxen (500)	他單一藥物繼續治療。（合併療法 NSAID 應避				
naproxen sodium (550-1100)	免使用超過 14 天）				
indobufen (400)					
lornoxicam (12)		B	+	?	III
Ibuprofen (400-800)					
肉毒桿菌素 botulinum toxin Type A	於陣發性偏頭痛無效，於慢性偏頭痛療效尚待證實	A	?	?	
其他 others (mg/d)					
estradiol (1.5-3)	~ 可用於月經期重度偏頭痛患者。	B	++	++	II
feverfew, B2, magnesium	~ 大劑量有效，輔助型療法（非替代）。	B	+~++	+~++	II
guanefacine (0.075-0.15)	~ Alpha-2 催動劑，次要選擇。	B	?	+	III
cyproheptadine (2-4)	~ 低劑量開始使用，有嗜睡副作用。	C	+	?	III

有效劑量參考範圍每人不同，建議從低劑量開始，逐漸增加至最有效劑量，最少使用 3-4 周，可持續 4-6 個月，減量後若復發可重複療程。

5. 非類固醇類抗發炎製劑（Non-steroid anti-inflammatory drugs）

巨集分析顯示，naproxen（500mg/d）或 sodium naproxen（550-1100mg/d）用於偏頭痛的預防具有中等療效，爲（B，II）藥物[1,2]。其他如 ketoprofen（150mg/d），mefenamic acid (1500mg/d)，aspirin（1300mg/d）亦爲（B，II）等級[3]，但腸胃不適反應大。至於 ibuprofen、diclofenac、ketorolac、sulindac、nabumetone 等，或 COX-2 選擇性抑制劑，仍無足夠證據可用於偏頭痛之預防[4]。

偏頭痛的急性及預防性治療準則比較

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非類固醇類抗發炎製劑(non steroid anti-inflammatory drugs, NSAID)：根據2012年AAN修正準則，naproxen、naproxen sodium、ketoprofen、ibuprofen用於偏頭痛的預防具有中等療效，為(B, II)等級，而mefenamic acid 為(C, III)，aspirin、indomethacin為(U, IV)等級療效不佳。至於其他藥物如 diclofenac、sulindac、COX-2等並無納入分析中。上述藥物劑量並無明載，主要是根據284篇發表的臨床分析所做成之實證參考，研究等級不盡相同，僅15篇為class I水準。至於2009年EFNS準則，則以naproxen為(B, II)推薦等級，劑量為500-1000mg/d，aspirin為(C, III)，建議劑量為300mg/d。雖然依據臨床經驗，NSAID類止痛藥不建議長期給予病人服用，然而如需使用，目前仍以naproxen sodium (550mg/ qd-bid)為(B, II)推薦用藥，並需定期監測肝、腎功能。

Part 2 NSAIDs as Preventive Tx_ Further Evidence

Naproxen in Prophylaxis of Migraine

Dewey K. Ziegler, MD, David J. Ellis, MD, PhD

(*Arch Neurol* 1985;42:582-584)

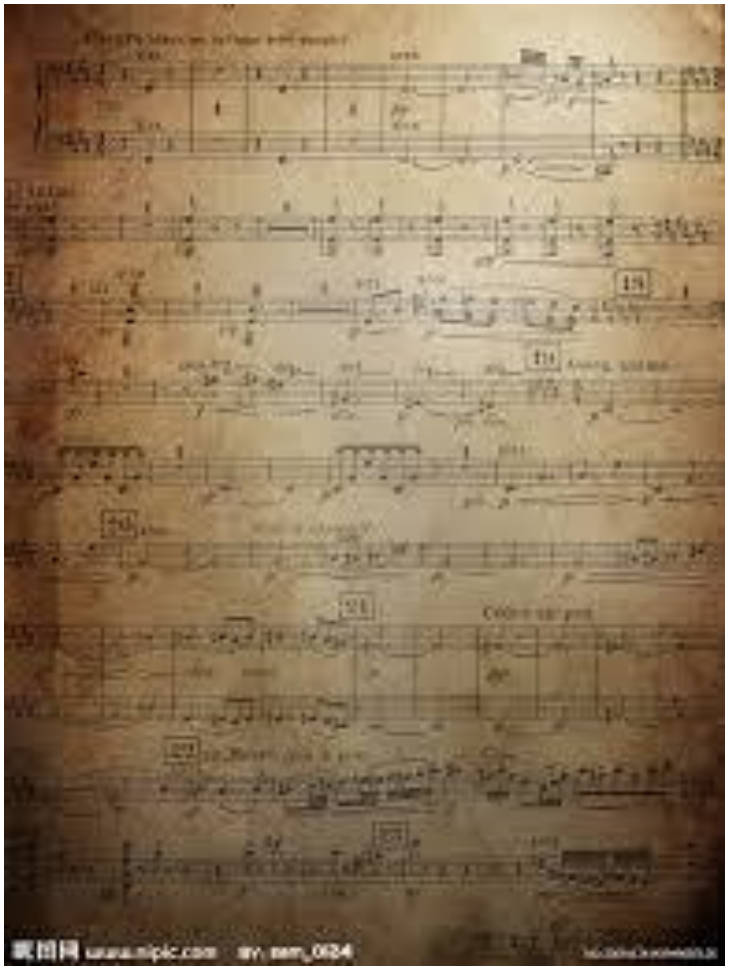
Successful migraine prophylaxis with naproxen sodium

K.M.A. Welch, MD; D.J. Ellis, MD; and P.A. Keenan

NEUROLOGY 35 September 1985

A Comparative Study of Naproxen Sodium, Pizotyline and Placebo in Migraine Prophylaxis

(*Headache* 30:710-715, 1990)



Naproxen in Prophylaxis of Migraine

Dewey K. Ziegler, MD, David J. Ellis, MD, PhD

N=40→34
Record diary
Rescue Mx

#Naproxen 550mg
(2#) bid X 2 months

Table 1.—Study Design

	Weeks 1-2	Weeks 3-10	Weeks 11-12	Weeks 13-20
Design	Single-blind	Double-blind	Single-blind	Double-blind
Medication	Placebo (introductory)	Naproxen sodium	Placebo (washout)	Naproxen sodium

(*Arch Neurol* 1985;42:582-584)

衛署藥製字第 015387 號

能百鎮錠 250 公絲(那普洛仙)

Naposin Tablets 250 mg (Naproxen)

識別：D31

本製劑爲非類固醇消炎劑，屬於芳香乙酸類衍生藥物，爲一種全身性抗炎劑。實驗證明其抗炎作用與鎮痛作用爲同類製劑之數倍。口服吸收迅速，血漿中半生期 10~17 小時，可有效地解除風濕性關節炎症狀。

成分：每錠含有：Naproxen 250mg

用法及用量：本藥須由醫師處方使用。

1.風濕關節炎、骨關節炎、腰痛、脊椎炎、滑囊炎等肌肉與骨骼疾患：一般治療劑量每日 500~1000mg 分 2 次(間隔 12 小時)服用，早晨及晚間之用量視主要症狀而定，即夜間疼痛或晨間僵直。

下列情況起初三週之建議每日劑量 750~1000 mg：

(1)嚴重夜間疼痛及晨間僵直。

(2)由高劑量之其他抗風濕劑改用本品時。

(3)以疼痛爲主要症狀之骨關節炎。

2.急性痛風：立即使用 750mg，然後每 8 小時服 250mg，直至症狀消失。

3.幼年型關節炎：每日總劑量 10mg/kg 分二次服用。

4.其他病症：立即服 500mg，然後每 6~8 小時服 250mg。

Naproxen in Prophylaxis of Migraine

Dewey K. Ziegler, MD, David J. Ellis, MD, PhD

Table 2.—Overall Rating of Therapeutic Effectiveness*

	Period		
	Naproxen Sodium	Placebo	P
Investigator rating			
Median	3.00	2.00	.02
Mean	2.53	2.00	. . .
SD	1.16	0.98	. . .
Patient rating			
Median	3.00	2.00	.01
Mean	2.56	1.97	. . .
SD	1.18	0.97	. . .

*Global assessment was rated as follows: 4, very good; 3, good; 2, fair; and 1, poor.

Table 3.—Calculation of Indexes From Patient Daily Records*

Index	Calculation
Severity	{[(No. of Days With Mild Rating) + (2 × No. of Days With Moderate Rating) + (3 × No. of Days With Severe Rating)] / (No. of Days in Period)} × 7
Duration	[(Hours of Duration Summed Over Period) / (No. of Days in Period)] × 7
Severity × duration	{[(Severity Rating × Hours) Summed Over Period] / (No. of Days in Period)} × 7
Medication	[(No. of Days With Therapeutic Medications) / (No. of Days in Period)] × 7

*Values are multiplied by a factor of 7 so that the results can be reported on a per-week basis.

Table 4.—Patient Daily Record Variables

	Period		
Index	Naproxen Sodium	Placebo	P
Severity			
Median	2.24	3.06	.004
Mean	2.79	3.82	. . .
SD	2.47	2.73	. . .
Duration, hr / wk			
Median	7.71	12.96	.02
Mean	16.14	22.53	. . .
SD	18.68	21.28	. . .
Severity × duration			
Median	15.86	27.19	.02
Mean	27.89	40.74	. . .
SD	30.40	36.86	. . .
Activity reduction			
Median	0.74	1.38	.05
Mean	1.16	1.68	. . .
SD	1.37	1.34	. . .
Medications, days / wk			
Median	0.98	1.60	.01
Mean	1.43	1.88	. . .
SD	1.50	1.51	. . .

(*Arch Neurol* 1985;42:582-584)

Naproxen in Prophylaxis of Migraine

Dewey K. Ziegler, MD, David J. Ellis, MD, PhD

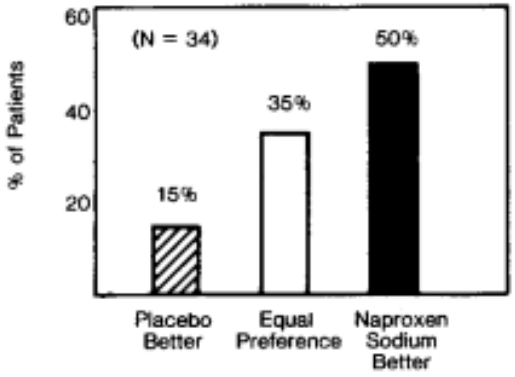


Fig 1.—Patient treatment preference.

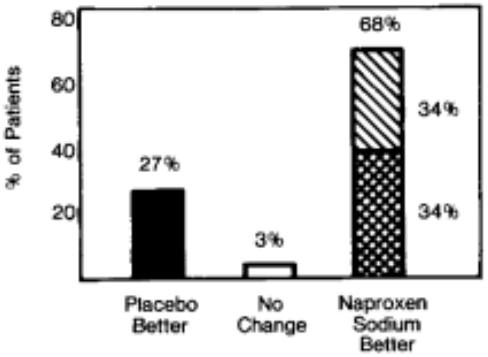


Fig 3.—Reduction in use of analgesic medications. Top portion of third bar represents patients who had more than 50% reduction in analgesic use during treatment with naproxen; bottom portion, patients who had less than 50% reduction.

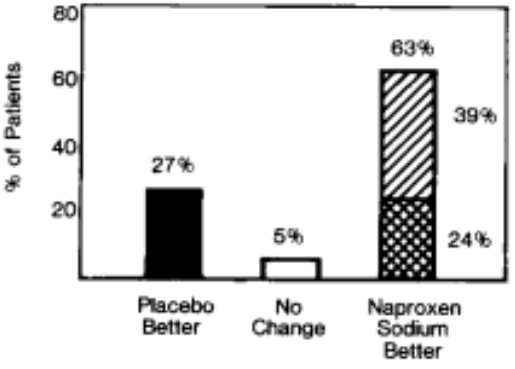


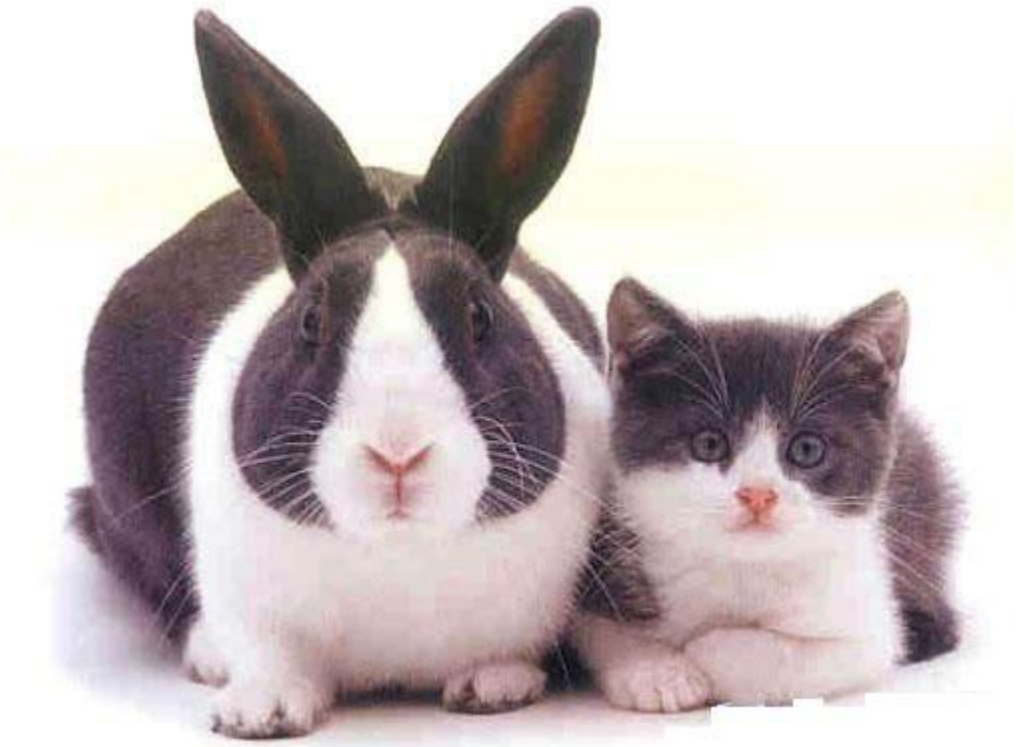
Fig 2.—Reduction in severity index. Top portion of third bar represents patients who had more than 50% reduction in severity index during treatment with naproxen; bottom portion, patients who had less than 50% reduction.

Table 5.—Adverse Reactions (N = 40)

	Period*		
	Naproxen Sodium	Placebo	Introductory Placebo
No. of patients reporting adverse reactions	5	7	4
No. of adverse reactions reported	7	8	7
Type of reaction, No. of patients			
Gastrointestinal tract symptoms	4	4	2
Drowsiness	1	1	0
Aches and pains	0	1	1
Other†	0	2	3

*No adverse reactions were reported during the washout period.
†Including incoordination, slurred speech, blurred vision, hypertension, and itching.

(*Arch Neurol* 1985;42:582-584)



Successful migraine prophylaxis with naproxen sodium

K.M.A. Welch, MD; D.J. Ellis, MD; and P.A. Keenan

Table 1. Patient demographies

Variable & parameter	Drug sequence group: Active to placebo (N = 16)	Drug sequence group: Placebo to active (N = 17)	All patients combined (N = 33)
Sex			
No. (%) female	15 (94%)	14 (82%)	29 (88%)
No. (%) male	1 (6%)	3 (18%)	4 (12%)
Age			
Mean ± SD	41.1 ± 15.4	36.4 ± 8.6	38.7 ± 12.4
(Min, max)	(22, 71)	(22, 48)	(22, 71)
Type of migraine			
No. (%) common	13 (87%)	15 (88%)	28 (88%)
No. (%) classic	2 (13%)	2 (12%)	4 (12%)

Table 2. Overall evaluation of prophylactic efficacy

Global assessment variables*	Anaprox period	Placebo period	*p* values: Drug effect	*p* values: Carry-over
Investigator response				
Median	2.00	1.00	0.03	0.52
Mean	2.15	1.64		
SD	1.06	0.87		
Patient response				
Median	2.50	2.00	0.03	0.64
Mean	2.45	1.92		
SD	1.21	1.02		

* Assessment rating: 1 = poor, 2 = fair, 3 = good, 4 = very good.

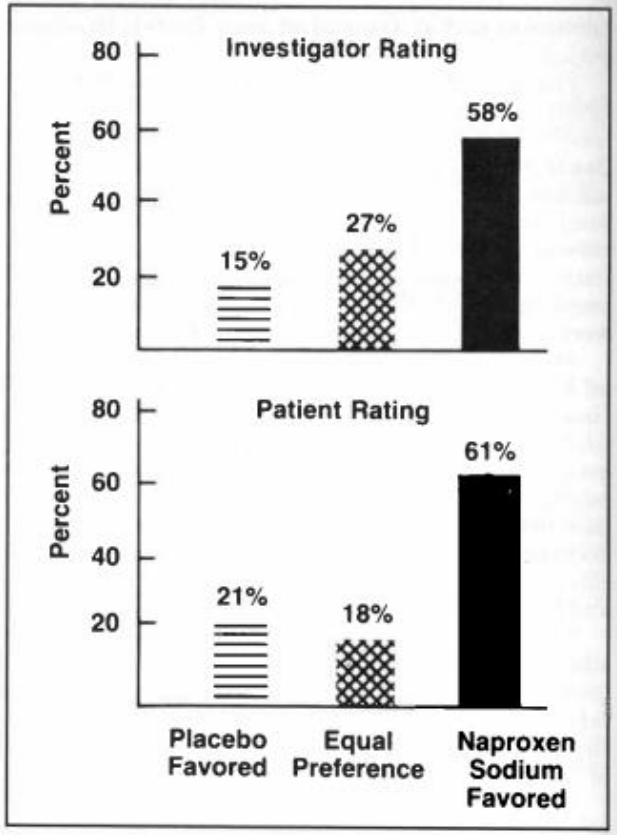


Figure 1. Comparative rating of prophylactic efficacy for each treatment period. The percentage number of patients that preferred naproxen sodium over placebo based on patient and investigator ratings.

the tachycardia. However, the patient requested Inderal and was removed from the study. The other AD

Successful migraine prophylaxis with naproxen sodium

K.M.A. Welch, MD; D.J. Ellis, MD; and P.A. Keenan

Table 3. Summary of Patient Daily Record indexes* (N = 31)

	Naproxen sodium period	Placebo period	p values† Drug effect	p values† Carry-over
Severity index				
Median	2.02	3.32	0.02	0.87
Mean	2.61	3.47		
SD	2.01	2.16		
Activity reduction index				
Median	1.15	1.98	0.002	0.11
Mean	1.73	2.60		
SD	1.54	2.03		
Nausea index				
Median	0.38	0.94	0.002	0.12
Mean	0.85	1.43		
SD	1.20	1.66		
Vomiting index				
Median	0.00	0.37	0.003	0.37
Mean	0.26	0.60		
SD	0.51	0.80		
Severity × duration				
Median	25.05	37.60	0.01	0.36
Mean	30.38	43.37		
SD	27.36	29.55		
Headache duration				
Median	15.38	20.02	0.03	0.53
Mean	17.49	21.63		
SD	15.76	13.03		
Days per week with therapeutic medications				
Median	1.50	1.72	0.02	0.91
Mean	1.55	2.08		
SD	1.19	1.55		

* Indexes defined in text.
† Nonparametric crossover analysis.

Table 4. Summary of days per week with headache (N = 31)

	Anaprox period	Placebo period	p values* Drug effect	p values* Carry-over
Days per week with any headache†				
Median	1.42	1.88	0.11	0.94
Mean	1.57	1.88		
SD	1.14	1.08		
Days per week with mild headache				
Median	0.50	0.66	0.80	0.19
Mean	0.76	0.75		
SD	0.70	0.68		
Days per week with moderate headache				
Median	0.50	0.51	0.35	0.78
Mean	0.58	0.68		
SD	0.50	0.74		
Days per week with severe headache				
Median	0.00	0.35	0.004	0.27
Mean	0.23	0.46		
SD	0.32	0.48		

* p values from nonparametric crossover analysis.
† Days per week = 7 × (No. days in period with headache)/(No. days in period).

Successful migraine prophylaxis with naproxen sodium

K.M.A. Welch, MD; D.J. Ellis, MD; and P.A. Keenan

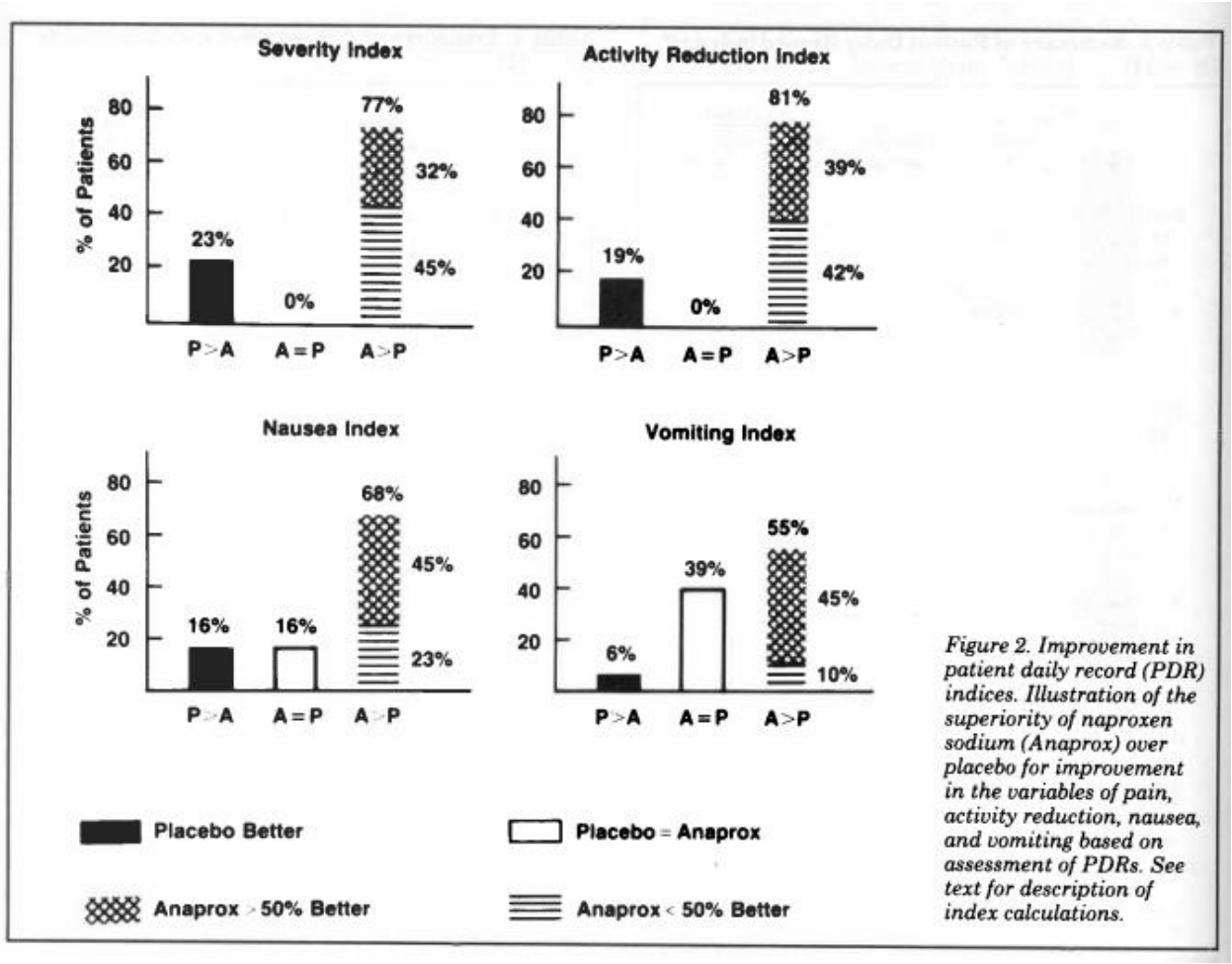


Figure 2. Improvement in patient daily record (PDR) indices. Illustration of the superiority of naproxen sodium (Anaprox) over placebo for improvement in the variables of pain, activity reduction, nausea, and vomiting based on assessment of PDRs. See text for description of index calculations.

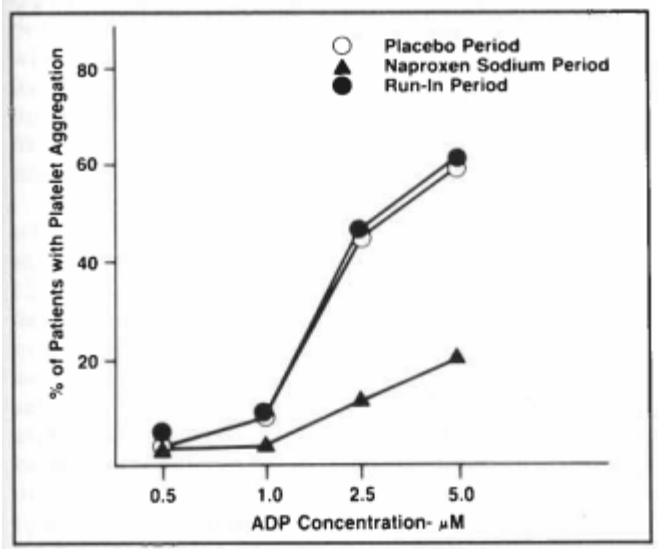
Successful migraine prophylaxis with naproxen sodium

K.M.A. Welch, MD; D.J. Ellis, MD; and P.A. Keenan

Table 5. Summary of adverse reactions

Parameter	All patients (N = 46)		
	Anaprox period	Placebo period	Run-in period
Number of patients reporting adverse reactions	9	9	2
Number of adverse reactions reported	14	14	3
Number of adverse reactions			
Probably related Rx	3	0	0
Probably not related Rx	9	12	3
Unknown relationship Rx	1	1	0
Relationship not stated	1	1	0
Number of patients reporting			
GI problems	6	3	2
Dizziness/faintness	2	0	0
Pains	1	2	0
Urinary problems	1	1	0
Other	1	3	0

Note: No adverse reactions were reported during the placebo washout.



Successful migraine prophylaxis with naproxen sodium

K.M.A. Welch, MD; D.J. Ellis, MD; and P.A. Keenan

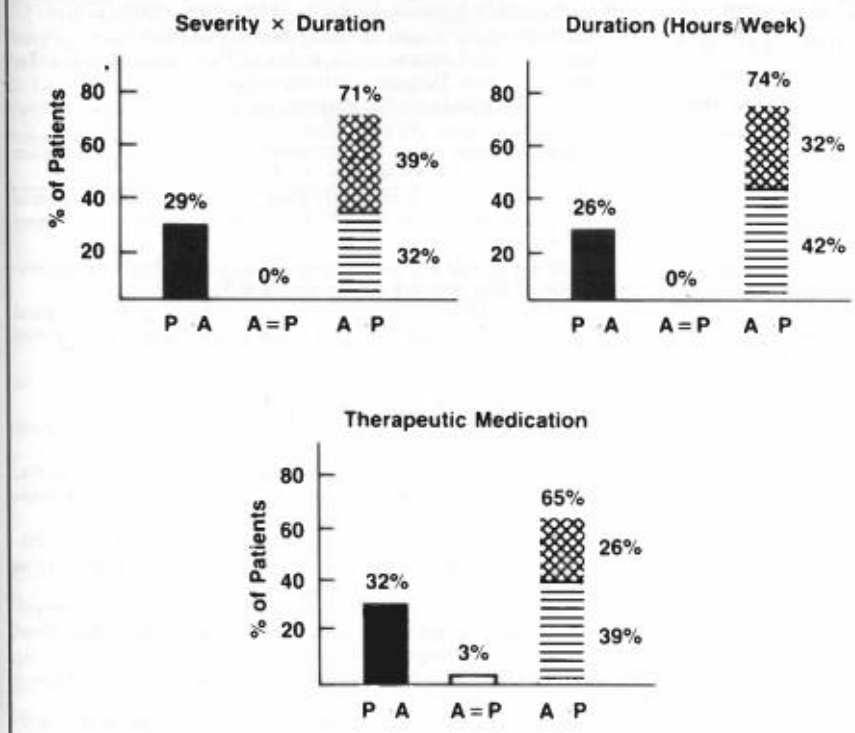
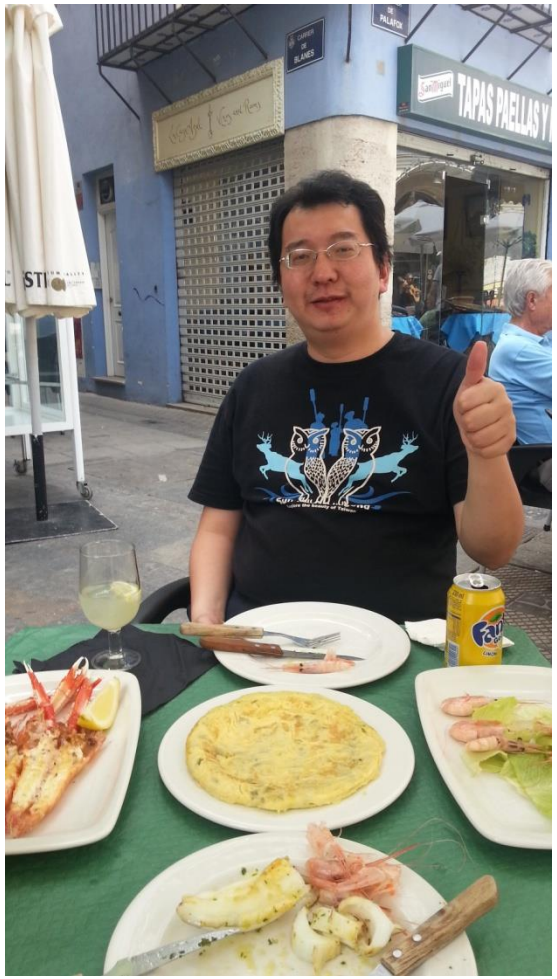


Figure 3. Improvement in patient daily record (PDR) indices. To illustrate the superiority of naproxen sodium (Anaprox) over placebo for improvement in the variables of duration, duration of severity, and usage of analgesic medications based on assessment of PDRs. See text for description of index calculations.

變換口味~~

Discussion. Indomethacin was the first anti-prostaglandin drug to be used in a satisfactorily controlled trial in migraine prophylaxis; it was ineffective.[13] At that time, the prostaglandin effects of the drug were unrecognized. Later, ketoprofen proved to be a mildly effective preventative,[14] but salicylate therapy was permitted when patients had acute headache. Success was also obtained with aspirin in combination with dipyridamole, but the study had few subjects, a high dropout rate, and concurrent medications included estrogens, antidepressants, and anxiolytics.[15] Naproxen has been studied previously in a double-blind, placebo-controlled, crossover manner in doses of 250 mg twice a



A Comparative Study of Naproxen Sodium, Pizotyline and Placebo in Migraine Prophylaxis

Table 1
Migraine Indices

- **Headache Unit Index =** $\frac{\text{number of migraine episodes}}{\text{number of treatment days}}$

(frequency of attacks)

- **Corrected Headache Unit Index =**

$$\frac{\text{Sum of (severity x duration of each episode)}}{\text{number of treatment days}}$$

Severity scale:
1 = Slight
2 = Moderate
3 = Severe

Duration scale:
1 = < 8 hours
2 = 8-16 hours
3 = > 16 hours but < 24

- **Pain intensity rating** =

$$\frac{\text{Sum of (intensity level x number of episodes at that level)}}{\text{number of migraine episodes during treatment days}}$$

Intensity scale:
1 = Slight
2 = Moderate
3 = Severe

- **Severity of Disability Rating** =

$$\frac{\text{Sum of (level of disability x number of episodes at that level)}}{\text{number of migraine episodes during treatment days}}$$

Disability scale:
1 = No reduction in activity
2 = Moderate reduction in activity
3 = Unable to work/confined to bed

- **Rescue Medication Index =**

$$\frac{\text{Sum of (number of doses x strength of rescue medication)}}{\text{number of treatment days}}$$

Strength scale:
1 = Non-narcotic analgesics or benzodiazepines
2 = Narcotic analgesics
3 = Ergot compounds

(*Headache* 30:710-715, 1990)

A Comparative Study of Naproxen Sodium, Pizotyline and Placebo in Migraine Prophylaxis

Table 2
Mean Migraine Indices During Placebo Lead-in and Treatment Periods

	Naproxen Sodium		Pizotyline		Placebo	
	Lead-in	R_X	Lead-in	R_X	Lead-in	R_X
1. Headache unit index, #/week	1.58	0.92*	1.53	0.98*	1.64	1.46
2. Corrected headache unit index, #/week	5.31	2.85*	5.77	3.27	5.56	5.08
3. Pain intensity rating	2.02	1.64	1.97	1.80	1.98	1.86
4. Severity of disability rating	1.89	1.58	1.86	1.67	1.90	1.77
5. Rescue medication index	5.22	2.89*	4.68	3.20	5.83	5.10
6. Average duration of headache	1.66	1.35	1.67	1.59	1.58	1.55
7. Days incapacitated, #/week	0.31	0.18*	0.24	0.18	0.31	0.34
8. Migraines requiring rescue medication, #/week	1.21	0.73*	1.16	0.82	1.47	1.26
9. Vomiting episodes #/week	0.18	0.25	0.17	0.08	0.21	0.48

* Indicates change from baseline relative to placebo was statistically significant ($p < 0.0166$) using the Kruskal-Wallis test.

(*Headache* 30:710-715, 1990)

A Comparative Study of Naproxen Sodium, Pizotyline and Placebo in Migraine Prophylaxis

Table 3
Summary of Efficacy Outcome

Parameters	Naproxen Sodium Better then Placebo	Pizotyline Better than Placebo	Naproxen Sodium Better than Pizotyline
• Headache unit index	mth 1,2,3	mth 1,3	ns
• Corrected headache unit index	mth 1,2,3	mth 2	ns
• Pain intensity	mth 1	ns	ns
• Severity of disability	mth 1	ns	ns
• Rescue medication	mth 1,2,3	ns	mth 1
• Average duration of headache	mth 1	ns	mth 1
• Days incapacitated	mth 1,2	mth 1	ns
• Migraines requiring rescue medication	mth 1,3	ns	mth 1
• Vomiting episodes	ns	ns	ns

ıs = not significant for months 1, 2 and 3.

(*Headache* 30:710-715, 1990)

A Comparative Study of Naproxen Sodium, Pizotyline and Placebo in Migraine Prophylaxis

Table 4
Number (Percentage) of Patients Reporting Side Effects During Treatment Period

	Naproxen Sodium N=58	Pizotyline N=58	Placebo N=56
• Gastrointestinal	8 (13.7%)	7 (12%)	3 (5.3%)
• CNS	4 (6.9%)	4 (6.9%)	5 (8.9%)
• Skin	2 (3.4%)	0	1 (1.7%)
• Weight gain	0	6 (10.3%)	1 (1.7%)
• Other	4 (6.9%)	2 (3.4%)	4 (7.1%)

(*Headache* 30:710-715, 1990)

Mini-Prophlaxis for Menstrual Migraine

Naproxen Sodium in Menstrual Migraine Prophylaxis: A Double-Blind Placebo Controlled Study

G. Sances, E. Martignoni, L. Fioroni,* F. Blandini, F. Facchinetti* and G. Nappi

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Accepted for Publication: September 30, 1990.

SYNOPSIS

In this study, the efficacy of Naproxen sodium (Nxs) in the prophylaxis of Menstrual Migraine (MM) was tested, versus Placebo (PL). Forty women suffering from MM were admitted to a double-blind treatment protocol with Nxs 550 mg twice each day by mouth or Placebo (PL), for 3 months; in the next 3 months all the women were treated with the active drug in an open study. The headache intensity and duration, as well as the number of days of headache and the analgesic consumption, were significantly reduced with Nxs compared to PL.

The efficacy of Nxs, shown also in improving premenstrual pain, and its good tolerability, support the use of this drug in the prophylactic therapy of MM.
Key words: menstrual migraine, prophylaxis, naproxen, NSAID.

(*Headache* 30:705-709, 1990)

Low-Dose Aspirin for Migraine Prophylaxis

Julie E. Buring, ScD; Richard Peto, FRS; Charles H. Hennekens, MD

The Physicians' Health Study is a randomized, double-blind, placebo-controlled trial that studied low-dose aspirin (325 mg every other day) therapy among 22 071 US male physicians aged 40 to 84 years. Annual follow-up questionnaires requested information on the occurrence of numerous medical conditions including migraine. At the end of 60 months, morbidity follow-up was 99.7% complete, and the reported consumption of aspirin or other platelet-active drugs was 86% in the aspirin group and 14% in the placebo group. Of those randomized to aspirin, 661 (6.0%) reported migraine at some time after randomization, as compared with 818 (7.4%) of those allocated to the placebo group, representing a statistically significant 20% reduction in recurrence rate. The rate of self-report of ordinary headache was similar in the two groups. These data indicate that migraine is mediated, at least in part, by the effects of platelets and suggest that low-dose aspirin should be considered for prophylaxis among those with a history of established migraine.

(*JAMA*. 1990;264:1711-1713)

Table 1.—Baseline Characteristics of Participants in the Randomized Treatment Groups*

	Aspirin (N = 11 037)	Placebo (N = 11 034)
Age, y	53.2 ± 9.5	53.2 ± 9.5
History of hypertension, %†	14.0	13.9
Systolic blood pressure, mm Hg	126.2 ± 12.0	126.1 ± 11.7
Diastolic blood pressure, mm Hg	78.9 ± 7.5	78.8 ± 7.5
History of high level cholesterol, %‡	7.0	6.8
Cholesterol level, mmol/L	5.48 ± 1.15	5.48 ± 1.18
History of diabetes, %	2.5	2.3
History of angina, %	1.4	1.2
Parental myocardial infarction, %	13.0	13.1
Current smoking, %	11.0	11.1
Past smoking, %	39.7	39.1
Daily alcohol use, %	24.9	24.9
Exercise more than once per week, %	72.5	72.0
Body-mass index, kg/m²	24.9 ± 3.1	24.9 ± 3.0
Multivitamin use, %	19.9	19.9

(*JAMA*. 1990;264:1711-1713)

Table 2.—Aspirin and Migraine in the Physicians' Health Study: Reports of Migraine After Randomization

	No. (%)			
	Aspirin (N = 11 037)	Placebo (N = 11 034)	*P*	Relative Risk (95% Confidence Interval)
Ever report of migraine	661 (6.0)	818 (7.4)	.00001	0.80 (0.72-0.88)
Report of migraine by follow-up questionnaire				
6 mo	216 (2.0)	271 (2.5)	.01	0.80 (0.67-0.95)
12 mo	273 (2.6)	324 (3.0)	.04	0.85 (0.72-0.99)
24 mo	302 (2.8)	400 (3.8)	<.001	0.76 (0.65-0.88)
36 mo	300 (2.8)	368 (3.5)	.01	0.81 (0.70-0.95)
48 mo	314 (3.0)	383 (3.7)	.01	0.82 (0.70-0.94)
60 mo	189 (2.7)	266 (3.8)	<.001	0.71 (0.59-0.85)
Ever report of headache	4237 (38.4)	4324 (39.2)	.13	0.97 (0.93-1.01)

(*JAMA*. 1990;264:1711-1713)

European Journal of Neurology 2006, 13: 560–572 doi:10.1111/j.1468-1331.2006.01411.x

EFNS TASK FORCE ARTICLE

EFNS guideline on the drug treatment of migraine – report of an EFNS task force

Members of the task force: S. Evers[a], J. Áfra[b], A. Frese[a], P. J. Goadsby[c], M. Linde[d], A. May[e] and P. S. Sándor[f]

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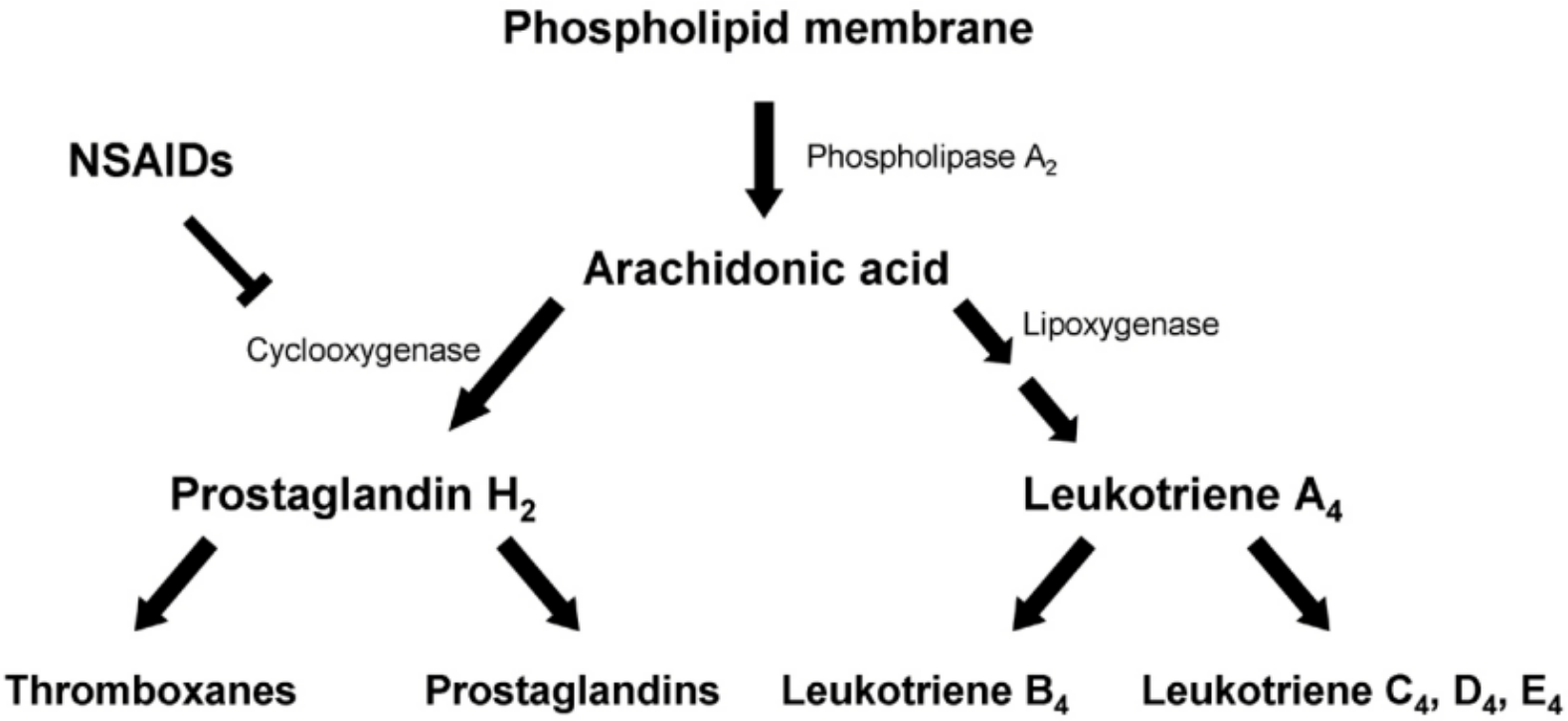
Group, Instit ; [d]Cephalea Pain Center, Läkarhuset
Södra vägen, amburg, Germany; and [f]Department of
Neurology, U

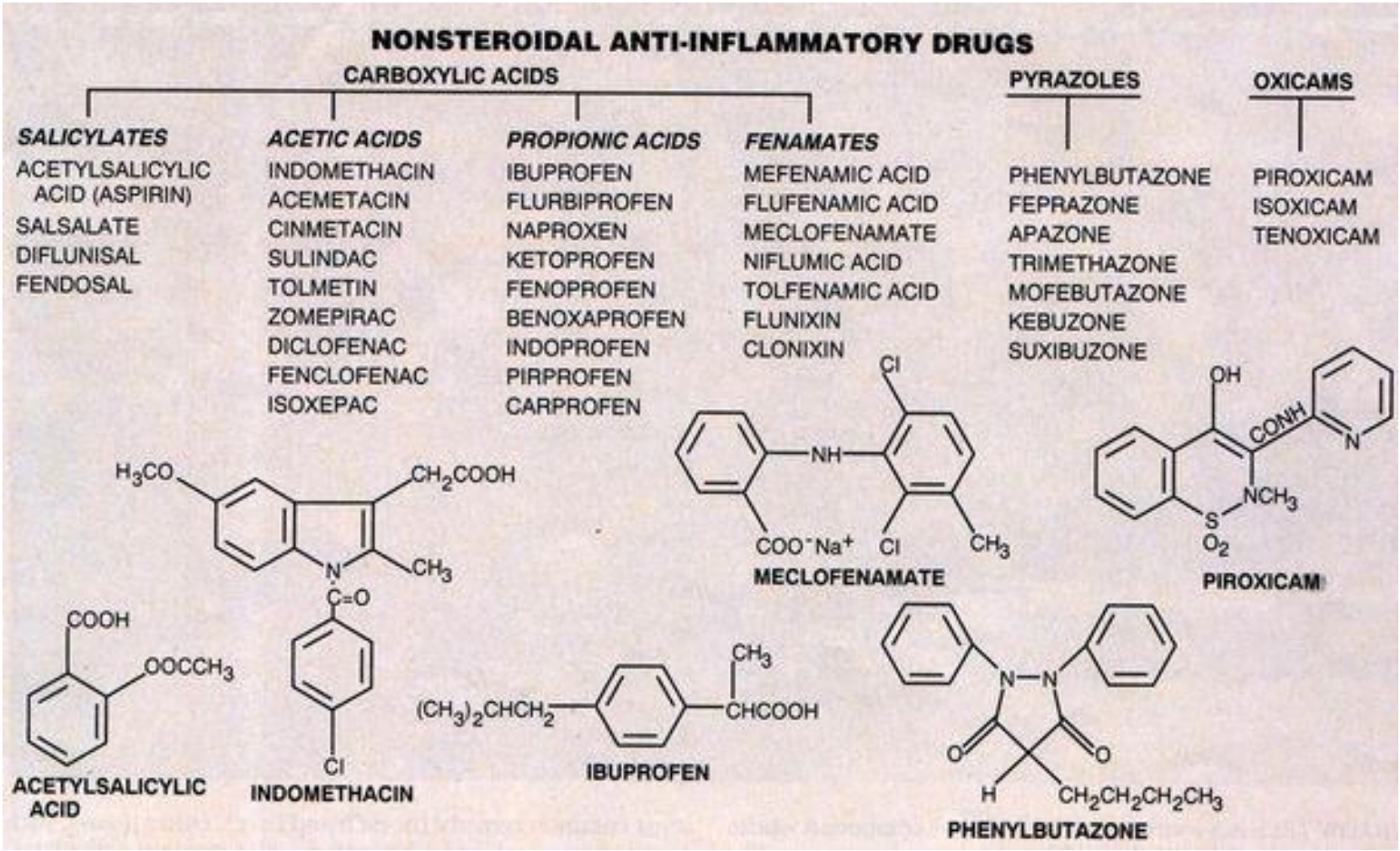
NSAIDs

In some comparative trials, ASA was equivalent to or worse than a comparator (which had shown efficacy in other trials) but never has achieved a better efficacy than placebo in direct comparison. However, in two large cohort trials, ASA 200–300 mg reduced the frequency of migraine attacks [110,111]. Naproxen 1000 mg was better than placebo in three controlled trials [112–114]. Moreover, tolfenamic acid showed efficacy in two placebo-controlled trials [115,116]. Other NSAIDs studied were ketoprofen, mefenamic acid, indobufen, flurbiprofen, and rofecoxib [117]. However, all studies for the later substances were small and had no sufficient design.

Aspirin 150-300mg qd



PGE= ECA dilatation
PGF2= Induced intracerebral artery constriction


NONSTEROIDAL ANTI-INFLAMMATORY DRUGS
CARBOXYLIC ACIDS
PYRAZOLES
OXICAMS
SALICYLATES
ACETYLSALICYLIC ACID (ASPIRIN)
SALSALATE
DIFLUNISAL
FENDOSAL
ACETIC ACIDS
INDOMETHACIN
ACEMETACIN
CINMETACIN
SULINDAC
TOLMETIN
ZOMEPIRAC
DICLOFENAC
FENCLOFENAC
ISOXEPAC
PROPIONIC ACIDS
IBUPROFEN
FLURBIPROFEN
NAPROXEN
KETOPROFEN
FENOPROFEN
BENOXAPROFEN
INDOPROFEN
PIRPROFEN
CARPROFEN
FENAMATES
MEFENAMIC ACID
FLUFENAMIC ACID
MECLOFENAMATE
NIFLUMIC ACID
TOLFENAMIC ACID
FLUNIXIN
CLONIXIN
PHENYLBUTAZONE
FEPRAZONE
APAZONE
TRIMETHAZONE
MOFEBUTAZONE
KEBUZONE
SUXIBUZONE
PIROXICAM
ISOXICAM
TENOXICAM
ACETYLSALICYLIC ACID
INDOMETHACIN
IBUPROFEN
MECLOFENAMATE
PIROXICAM
PHENYLBUTAZONE

非類固醇類消炎藥的藥動學性質及每日最高劑量						
		止痛作用		抗風溼作用		每日最
藥品	半衰期 (小時)*	開始作用 (小時)	作用時間 (小時)	開始作用 (天)	作用時間 (週)	高劑量 (mg)
短效						
Diclofenac	2	-	-	-	-	200
Ibuprofen	1.8-2.5	0.5	4-6	≦7	1-2	3200
Indomethacin	4.5	0.5	4-6	≦7	1-2	200
Ketoprofen	2-4	-	-	-	-	300
Mefenamic acid	2-4	-	-	-	-	1000
Mepirizole	1.5	-	-	-	-	600
Tiaprofenic acid	2.8-3.2	-	-	-	-	-
中效						
Fenbufen	9-12	-	-	≦7	-	1000
Naproxen	12-15	1	≦7	≦14	2-4	1500
Sulindac	7.8	-	-	<7	2-3	400
長效						
Piroxicam	30-86	1	48-72	7-12	2-3	20

Part 3 Medication Overuse Headache

- Story: morphine/tramadol in cancer patients
- ICHD-III criteria
- Mechanism

Subtypes of MOH

Ergotamine-overuse headache (8.2.1): Triptan-overuse headache (8.2.2): Opioid-overuse headache (8.2.4): Combination analgesic-overuse headache (8.2.5):	≥10 days per month on a regular basis for >3 months
Analgesic-overuse headache (8.2.3):	≥15 days per month on a regular basis for >3 months
Medication-overuse headache attributed to the combination of acute medications (8.2.6):	≥10 days per month on a regular basis for >3 months
Headache attributed to other medication overuse (8.2.7)	Regular overuse for >3 months of a medication other than those described above
Probable medication-overuse headache (8.2.8)	1. Overused medication has not yet been withdrawn 2. Medication overuse has ceased within the last 2 months but headache has not yet resolved or reverted to its previous pattern

MOH

Clinical features, pathophysiology, and treatment of medication-overuse headache

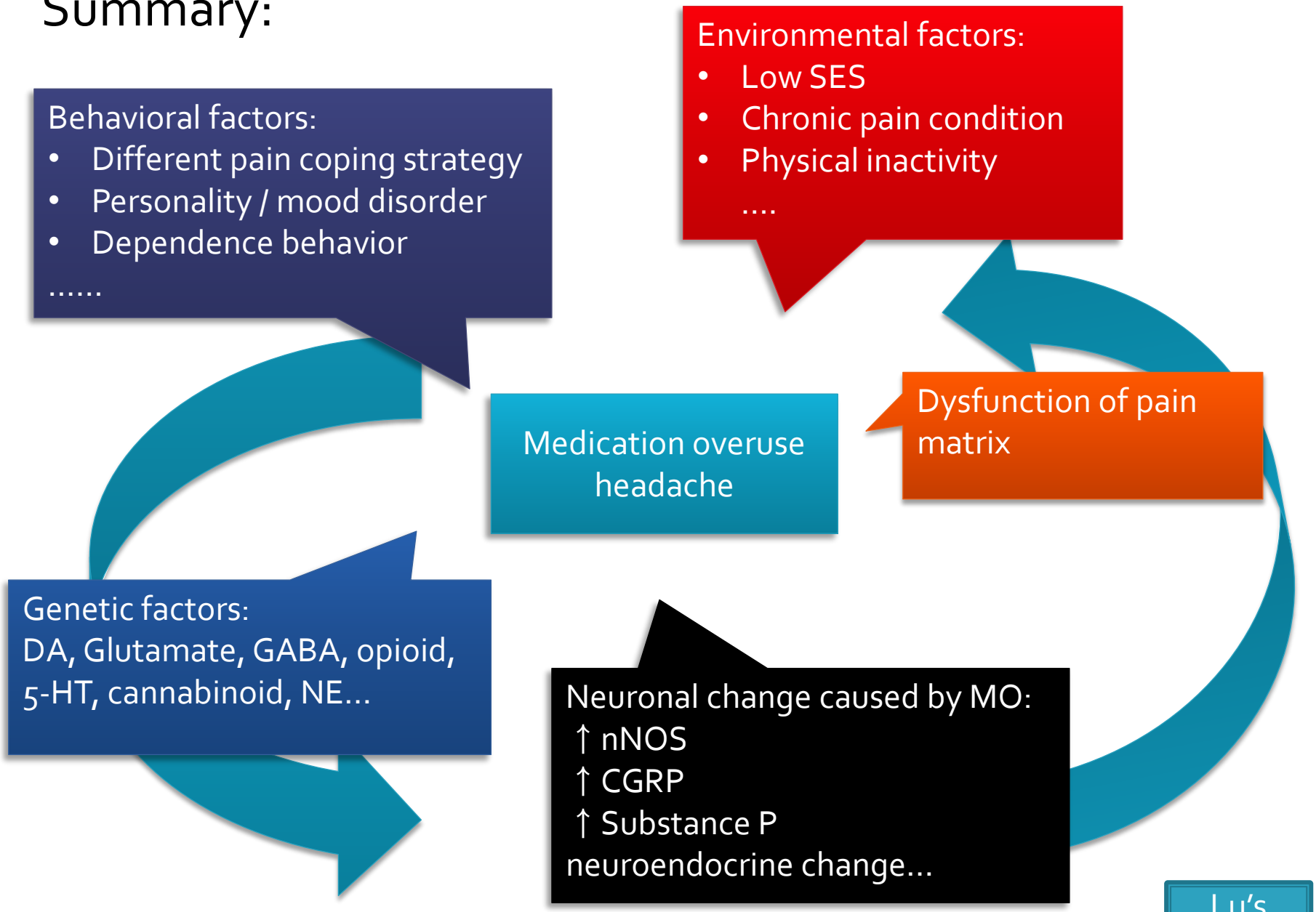
Stefan Evers, Martin Marziniak

Lancet Neurol 2010; 9: 391–401

- Neurophysiology: SSR
- Genetic Factors:
  Val66Met polymorphism, SLC6A3 under expression; also known as DAT1
- Endocrine and neurotransmitter function: orexin A and corticotrophin-releasing factor in the CSF

- Functional imaging: hypometabolism of the bilateral thalamus, anterior cingulate gyrus, insula/ventral striatum, and right inferior parietal lobe normalized 3 months later after quitted withdraw therapy
- Psychological mechanisms:
  →a subtype of drug addiction
  →patients with MOH were found to dislike analgesics but believed that they could not cope without them

Summary:


Environmental factors:
• Low SES
• Chronic pain condition
• Physical inactivity
....
Behavioral factors:
• Different pain coping strategy
• Personality / mood disorder
• Dependence behavior
.....
Medication overuse headache
Dysfunction of pain matrix
Genetic factors:
DA, Glutamate, GABA, opioid, 5-HT, cannabinoid, NE...
Neuronal change caused by MO:
↑ nNOS
↑ CGRP
↑ Substance P
neuroendocrine change...

Lu's

Risk factors for CM "Chronification"

Non modifiable

- older age
- female sex
- low education level
- worse socioeconomic status
- genetic factors

Modifiable

- Attack frequency
- Medication overuse
- Obesity
- Depression/anxiety
- Snoring/sleep apnea
- Stressful life events

Putative factors

- Proinflammatory or prothrombotic states

Current Pain Headache Report 2009; 13: 59-63

Concluison: severe migraine after r/o secondary headache

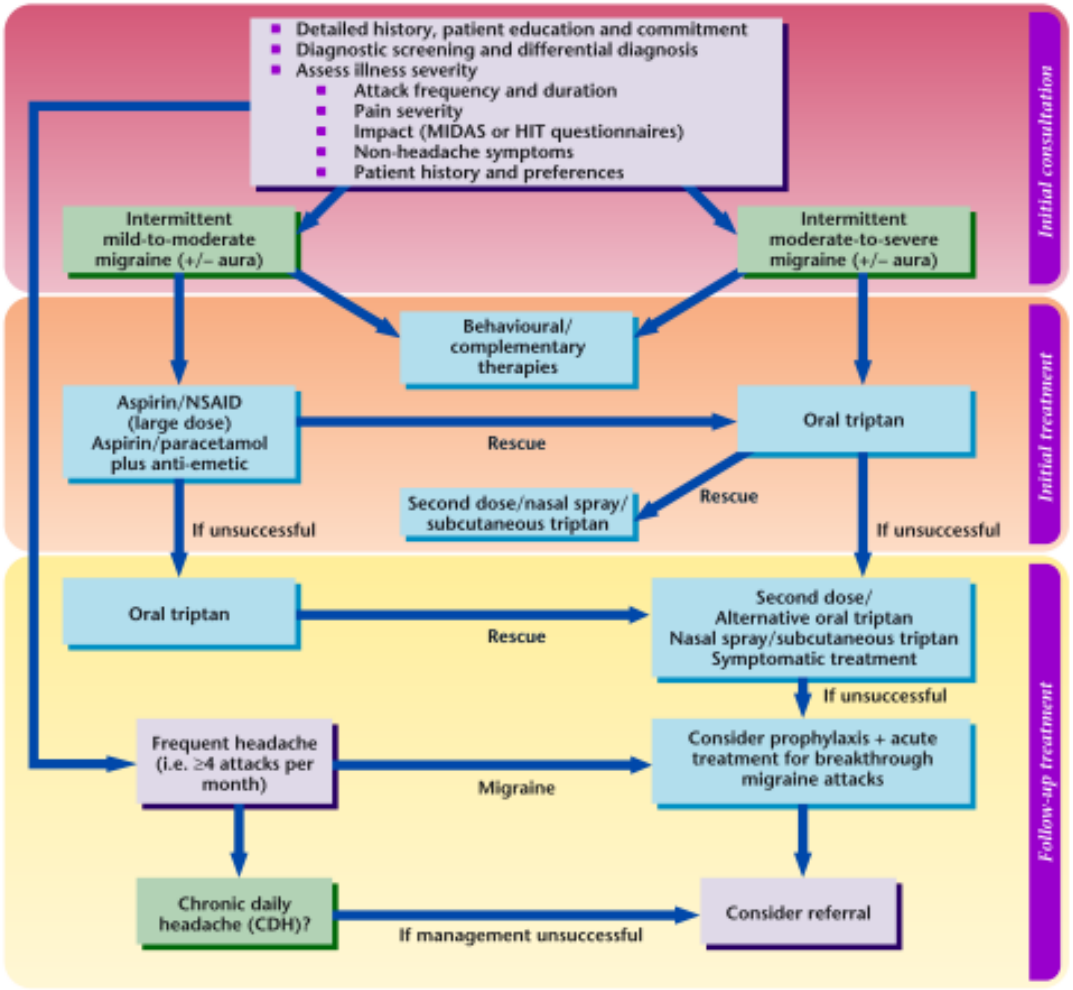
Dx: CDH? MOH?(Mx)

Well explained

NSAID+ PPI+

other Preventive Tx

Taperd NSAID after successful detoxifcation 2 weeks later



MIPCA

GP Algorithm

Table 1 Medications Used in the Abortive Management of Migraine

ASA, numerous generics 650–1,000 mg q 4–6 hours (maximum 4,000 mg daily) APAP (e.g., Tylenol) 325–1,000 mg q 4–6 hours (maximum 4,000 mg daily)	***Some combination OTC products*** • Anacin (ASA) 400 mg, caffeine 32 mg) • Bayer Extra Strength (APAP 500 mg, caffeine 32.5 mg) • Excedrin Extra Strength and Excedrin Migraine* (APAP 250 mg, ASA 250 mg, caffeine 65 mg) • Vanquish (APAP 194 mg, ASA 227 mg, caffeine 33 mg)
Barbiturate combinations* • Butalbital and ASA/caffeine (Fiorinal) 1–2 tablets q 4–6 hours (also available with codeine) • Butalbital and APAP/caffeine (Fioricet) 1–2 tablets q 4–6 hours (also available with codeine) Restrict use to avoid rebound; 4 tablets daily; not more than 2 days per week	***Serotonin receptor agonists (triptans)*** • Sumatriptan (Imitrex) Intranasal, Oral, SQ • Rizatriptan (Maxalt) Oral, MLT (dissolving product) • Zolmitriptan (Zomig) Oral, ZMT (dissolving product), Nasal • Naratriptan (Amerge) Oral • Almotriptan (Axert) Oral • Frovatriptan (Frova) Oral • Eletriptan (Relpax) Oral
Opiate combinations* • Propoxyphene with APAP (Darvocet) • Codeine with APAP (Tylenol #3) • Oxycodone with APAP or ASA (Percocet, Percodan) • Butorphanol nasal spray (Stadol) one spray in one nostril (1 mg); may repeat in 1 hour; maximum four sprays daily	***Ergot alkaloids*** • Dihydroergotamine mesylate (DHE) injection/1 mg/mL Nasal Spray (Migranol) • Ergotamine tartrate (numerous brands with various contents, including belladonna alkaloids, caffeine, and phenobarbital)
NSAIDs • Ibuprofen 200–400 mg q 4–6 hours (maximum 1,200 mg daily OTC) ◦ Advil Migraine Liqui-Gels ◦ Advil Migraine • Naproxen sodium 220 mg q 6–8 hours (maximum 660 mg daily), OTC Aleve • Numerous other products: diclofenac potassium (Cataflam), ketorolac (Toradol)	***Sympathomimetics**** • Isometheptene 65 mg, dichloralphenazone 100 mg, APAP 325 mg (Midrin)
Phenothiazines: prochlorperazine (Compazine), chlorpromazine (Thorazine), metoclopramide (Reglan)	***Anticonvulsants:*** IV valproate (Depacon)

APAP = acetaminophen; ASA = aspirin; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; SQ = subcutaneous.

* Regular weekly usage requires medical evaluation and determining the need for preventative therapy.

Adapted from references 10, 36, 41, 42, and 46.

偏頭痛預防性藥物治療準則

台灣頭痛學會治療準則小組

表.（續）偏頭痛的預防性治療藥物

藥物種類（有效劑量_mg/d）	在偏頭痛預防性治療中的注意事項	*證據強度	+臨床療效	^統計測量	%推薦等級
非類固醇類抗發炎製劑 NSAIDs	~NSAID 預防偏頭痛須注意腸胃道副作用，長期				
ketorprofen (150)	使用者需注意肝腎功能，劑量最好從最低開始。	B	+~++	+~++	II
aspirin (1300)	臨床上依個人情形使用（單一使用時需較高劑				
fenoprofen (600-1800)	量，在合併療法時可減半開始，或更低劑量）。				
mefenamic acid (1500)	合併療法發揮療效時，應先停止 NSAID，以其				
naproxen (500)	他單一藥物繼續治療。（合併療法 NSAID 應避				
naproxen sodium (550-1100)	免使用超過 14 天）				
indobufen (400)					
lornoxicam (12)		B	+	?	III
Ibuprofen (400-800)					
肉毒桿菌素 botulinum toxin Type A	於陣發性偏頭痛無效，於慢性偏頭痛療效尚待證實	A	?	?	
其他 others (mg/d)					
estradiol (1.5-3)	~可用於月經期重度偏頭痛患者。	B	++	++	II
feverfew, B2, magnesium	~大劑量有效，輔助型療法（非替代）。	B	+~++	+~++	II
guanefacine (0.075-0.15)	~Alpha-2 催動劑，次要選擇。	B	?	+	III
cyproheptadine (2-4)	~低劑量開始使用，有嗜睡副作用。	C	+	?	III

有效劑量參考範圍每人不同，建議從低劑量開始，逐漸增加至最有效劑量，最少使用 3-4 周，可持續 4-6 個月，減量後若復發可重

NSAIDs in migraine prophylaxis

Side effects

- Dyspepsia
- Erosive gastritis
- Peptic ulceration
- Occult gastrointestinal bleeding
- Hematologic complications

Precautions

- Hypersensitivity to aspirin or other NSAIDs
- Active gastrointestinal bleeding
- Peptic ulcer
- Liver disease
- Kidney disease
- Elderly patients
- Coagulopathies

Special indications

- Concurrent arthritis, dysmenorrhea, and stroke (specifically with aspirin)

West J Med
2000;173:341-345