

Headache Case Share



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History

- **蘇X春女士, 71-year-old woman**
- **Past history**
 - Coronary artery disease
 - Hypertension
 - Dyslipidemia
 - Medication: aspirin, ISMN, Lescol-XL, Aprovel
- **Chief complaints**
 - persistent headache for 1-2 months

History

- ❑ **Chronic headache for 4-5 years**
- ❑ **Chronic daily headache > 15/month criteria**
- ❑ **Favor Transformed Migraine**
 - D/D Chronic Tension Type Headache
- ❑ **Over bilateral fronto-temporal area (migrating)**
 - Radiation to bilateral temporo-parietal area
- ❑ **No visual aura, but episodic nausea/vomiting**
- ❑ **Esp. attack in the afternoon or after heavy work**
- ❑ **No postural related, no red eyes, no orbital pain**

Treatment

- **Acute headache abortive treatment**
 - Novamine + solaxin + Voltaren Treatment 3-5 days
- **Prophylactic treatment with Suzin (10) bid 2 weeks**
- **Then Suzin (10) 1# HS for 2-3 months**
- **Parkinsonism Slow motion & mask face noted**
- **No tremor, mild stoop posture**
- **DC Suzin => still slow motion**

European Federation of Neurological Societies

EFNS 2010 guideline on the drug treatment of migraine

Table. 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. Drugs of Second Choice for Migraine Prophylaxis (Evidence of Efficacy, but Less Effective or More Side Effects than Drugs of the Table above)

Substances	Daily Dose	Level
Amitriptyline	50–150	B
Naproxen	2 x 250–500	B
Petasites	2 x 75	B
Bisoprolol	5–10	B

Table. 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 x 6.25 mg	C
Riboflavin	400 mg	C
Coenzyme Q10	300 mg	C
Candesartan	16 mg	C
Lisinopril	20 mg	C
Methysergide	4–12 mg	C

Table 2 Summary of drugs recommended for migraine prophylaxis, with level of evidence for each European country

Country	UK (lines of recommendation)	Scotland (grades of recommendation)	Germany (strength of recommendation)	Croatia (rating of recommendation)	Spain (levels of evidence)	France (grading of recommendation)	Italy (levels of recommendation)
<i>β</i> -blockers							
Metoprolol	1	D	A	B	1	A	2
Propranolol	1	A	A	A	1	A	1
Atenolol	1	D	–	A	1	A	1
Bisoprolol	1 ^a	–	B	–	–	–	–
Nadolol		D	–	B	1	A	2
Timolol		D	–	–	–	A	–
Ca channel blockers							
Flunarizine	NA		A	A (NA)	1	A	1
Cinnarizine			–	–	–	–	2
Verapamil			–	B	–	–	2
Diltiazem			–	–	–	–	3a
Nimodipine			–	B	–	–	3a
Anti-epileptic drugs							
Valproic acid	2	A	A	A	1	A	1
Topiramate	2	A	A	B	1	A	2
Gabapentin	3	C	C	A	–	A	2
Lamotrigine	–	–	–	B	–	–	2

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
Serotonin antagonists					
Cyproheptadine	C	?	+	Frequent	3a
Methysergide	A	+++	+++	Frequent	4
Other					
Feverfew	B	++	+	Infrequent	2
Magnesium	B	+	+	Infrequent	2
Vitamin B2	B	+++	++	Infrequent	2

表. 偏頭痛的預防性治療藥物

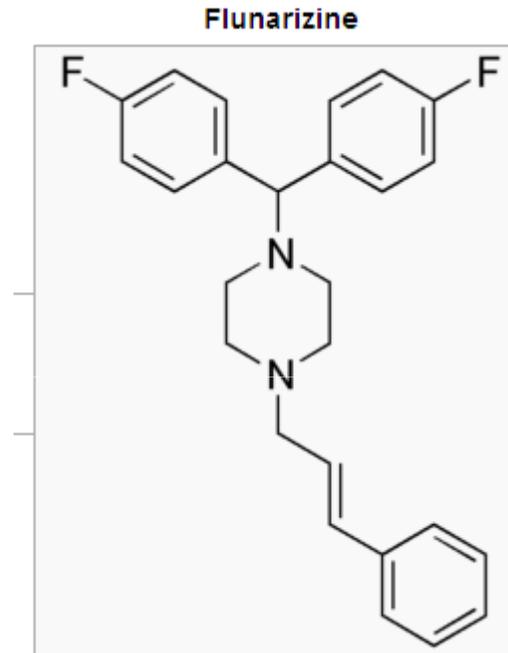
藥物種類 (有效劑量 mg/d)	在偏頭痛預防性治療中的注意事項	*證據強度	+臨床療效	^統計測量	%推薦等級
乙型阻斷劑 beta-blocker					
propranolol (20-160)	~ 用於偏頭痛預防優先選擇藥物, 但氣喘、心臟傳導阻滯、糖尿病、末梢血管疾病、憂鬱症患者應避免使用	A	+++	+++	I
atenolol (50-100)	~ acebutolol, pindolol 等有 intrinsic sympathomimetic activity (ISA) 之 beta blockers 預防偏頭痛無效.	B	++	++	II
metoprolol (50-200)		B	++	+++	II
nadolol (40-80)	~ 一次或分次服用。	B	+	+++	II
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, ER 長效型一天一次睡前, 一般型則需分次。	A	+++	+++	I
divalproex sodium (500-1000)	~ 注意肝臟代謝, 副作用水腫、肥胖。	A	+++	+++	I
valproic acid (300-1800)					
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, lamotrigine, clonazepam)	~ 此四類藥物, 用於預防偏頭痛療效不明, 不建議使用。	B	?	?	V
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用藥 (>12 歲)。老年人須注意錐體外副作用。	A	+++	+++	I
nimodipine (60-120)		B	+	+	II
verapamil (120-240)		B	+	+	II
diltiazem (?)		C	0	?	III

各國預防偏頭痛的用藥準則比較

國家	第一線	第二線	其他或輔助療法
台灣	β-blocker-Propranolol <u>CCB-Flunarizine</u>	TCA(三環抗抑鬱藥) 癲癇藥	
美國	β-blocker	TCA(三環抗抑鬱藥)	CCB/抗癲癇藥
英國	β-blocker 抗憂鬱劑 抗癲癇藥	血清素抑制劑	小白菊/鎂/B2 Co-Q10/針灸
法國	Propranolol Amitriptyline	<u>Flunarizine</u> Valproate/Topiramate Pizotifen	
德國	β-blocker –Propranolol/ Metoprolol <u>Flunarizine</u> Valproic acid/Topiramate (Grade A)	Bisoprolol (Grade B) Naproxen Petasites Amitriptyline	
歐盟	Propranolol/Metoprolol <u>Flunarizine</u> Valproic acid/Topiramate		

Flunarizine 為 (J&J PRD) Belgium 的 Janssen Pharmaceutica. 所開發

- 1967年研發出R14950物質
- 最早於1977年以商品名 Sibelium 上市
- **Clinical indication**
Peripheral Vertigo
- Mechanism:
 1. anti-histamine
 2. CCB



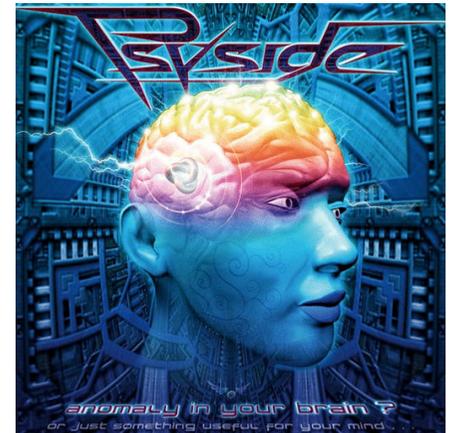
Systematic (IUPAC) name

1-[bis(4-fluorophenyl)methyl]-4-[(2E)-3-phenylprop-2-en-1-yl]piperazine

Formula C₂₆H₂₆F₂N₂

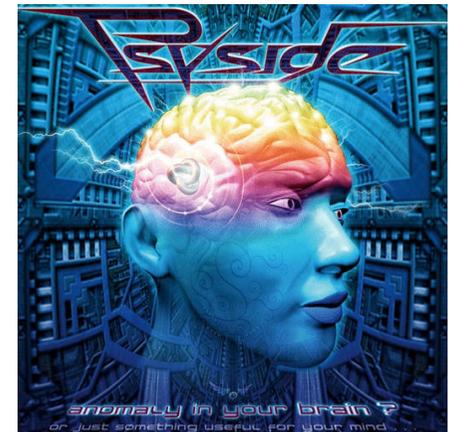
Flunarizine 用法用量

- 適應症：末梢循環障礙、暈動病、噁心、眩暈、迷路障礙
- 說明：預防典型偏頭痛(有前兆的)或普通型偏頭痛(沒有前兆的)。
前庭功能系統異常引起的前庭眩暈症狀治療。
- 偏頭痛之預防：
 - 1.開始劑量：65歲以下患者每天10mg(睡前)，65歲以上患者每天5mg。
 - 2.維持療法：可每星期連續服藥5天，休息兩天之維持療法。若維持效果相當好，且耐受性佳，6個月後可停止用藥。
- 通常給藥應在晚上，以減少想睡之副作用



Flunarizine Mechanism & Side Effect

- 作用機轉：Flunarizine為一種具有**選擇性鈣離子通道阻斷劑**及**抗組織胺**雙重作用的藥物。細胞在過度缺血及缺氧時，常造成細胞內鈣離子的過度負荷，進而使細胞損壞。Flunarizine在細胞正常狀態下，不會影響鈣離子的恆定，但在細胞受到刺激時，可以選擇性的阻止過多的鈣離子流入細胞中，避免細胞內鈣離子過度負荷。
- 有**阻止內因性痙攣物質**（如腎上腺素、多巴胺、血管緊張素、血管加壓素）導致血管收縮的作用，並可減少組織胺、血清素所引起之微血管緊張力不足的情形。
- 副作用：包括鎮靜、嗜睡、疲倦、體重的增加、齒齦增生、噁心、胸口灼熱、胃痛、失眠、焦慮、口乾、肌肉痛、皮膚發紅等。
- 使用禁忌：**有抑鬱病史、或目前有帕金森氏症及其他錐體束外異常之患者**



Some drugs developed by Janssen Pharmaceutica

R-code	Name	Brandname	Synthesized	Marketed
R5	ambucetamide	Neomeritine	1953	1955
R79	isopropamide iodide	Priamide-Janssen	1954	1955
R253	diisopromine	Bilagol	1955	1956
R516	cinnarizine	Stugeron	1955	1958
R875	dextromoramide	Palfium	1955	1957
R1132	diphenoxylate	Reasec	1956	1960
R1625	haloperidol	Haldol	1958	1959
R2498	trifluoperidol	Triperidol	1959	1961
R3345	pipamperone	Dipiperon	1960	1961
R3365	piritramide	Dipidolor	1960	1967
R4263	fentanyl	Fentanyl	1960	1963
R4584	benperidol	Frenactyl	1961	1965
R4749	droperidol	Dehydrobenzperidol	1961	1963
R4845	bezitramide	Burgodin	1961	1971
R6218	fluspirilene	Imap	1963	1971
R6238	pimozide	Orap	1963	1970
R7904	lidoflazine	Clinium	1964	1969
R11333	bromperidol	Impromen	1966	1981
R12564	levamisole	Ergamisol	1966	1969
R13672	haloperidol decanoate	Haldol decanoas	1967	1981
R14889	miconazole nitrate	Daktarin	1967	1971
R14950	flunarizine	Sibelium	1967	1977
R15889	lorcainide	Remivox	1968	1983

Table 1 Clinical classification of calcium antagonists

<i>Type I</i>	<i>Calcium antagonists with in vivo myocardial, electrophysiologic and vascular effects</i> Verapamil Gallopamil (D-600)	Diltiazam Tiapamil
<i>Type II</i>	<i>Calcium antagonists with predominant vascular effects in vivo (dihydropyridines)</i> Nifedipine Nitrendipine Nisoldipine Nimodipine	Nicardipine Niludipine Felodipine
<i>Type III</i>	<i>Calcium antagonists with selective vascular effects (piperazines)</i> Cinnarizine Flunarizine	
<i>Type IV</i>	<i>Calcium antagonists with complex pharmacologic profiles</i> Bepidil Lidoflazine	Perhexilene

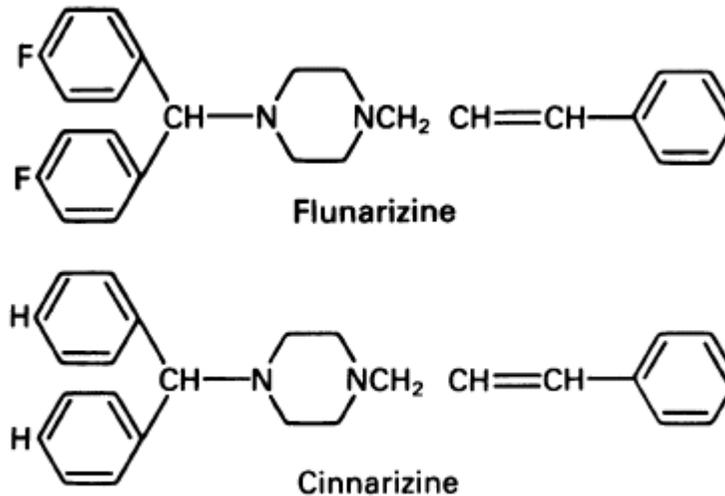
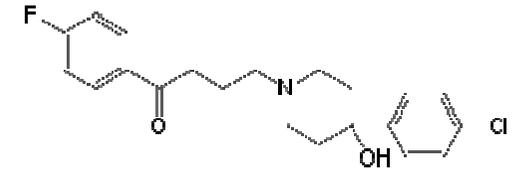
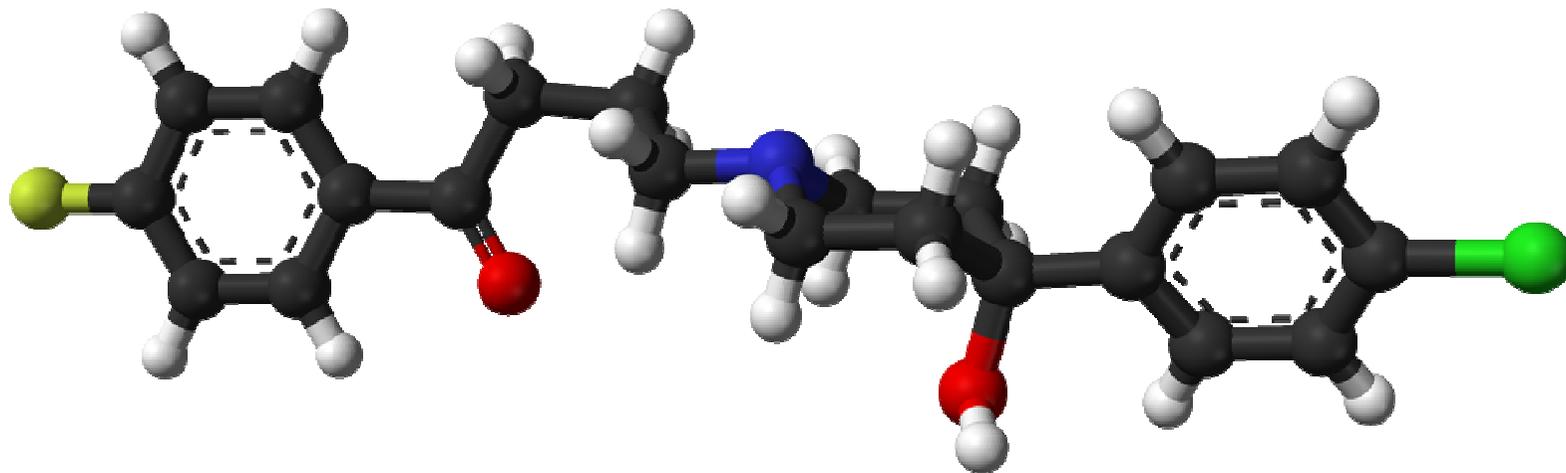
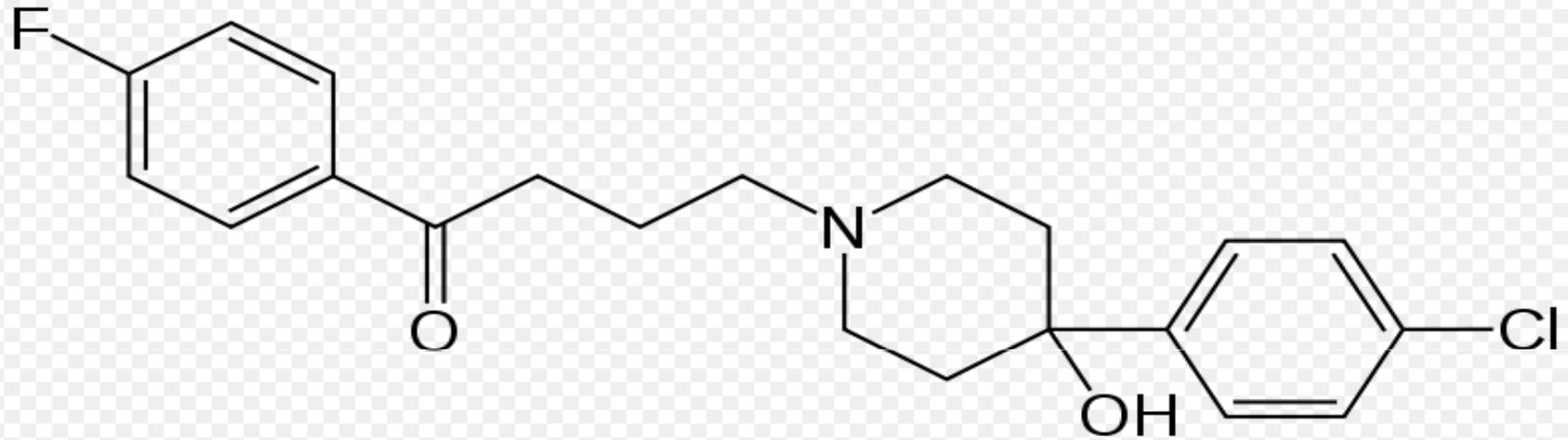


Figure 3 Structure of flunarizine and cinnarizine. These agents have a specificity for vascular tissues.



Haloperidol





Thank you for your attention!