2021 慢性偏頭痛診斷與治療訓練課程

時間：110 年 04 月 11 日(星期日) AM 08:30 ～ PM 17:00
地點：台中裕元花園酒店溫莎廣場 (地址: 台中市西屯區台灣大道四段 610 號)
主辦單位：台灣頭痛學會
協辦單位：台灣神經學學會、台灣愛力根藥品股份有限公司

Time	Topic	Speaker	Moderator
08:30-09:00	Registration	秘書處	
09:00-09:10	Opening Remarks	陳韋達 理事長 台灣頭痛學會	
09:10-09:40	Headache evaluation and classification	楊鈞百 主任 光田綜合醫院 神經內科	林高章 主任 奇美醫院 全人醫療科/神經內科
09:40-10:10	Diagnosis and Treatment of Chronic Migraine	黃子洲 副院長 台南活水診所 神經內科	施景森 主任 高雄榮總 神經內科
10:10-10:40	New Treatment of Chronic Migraine in Clinical Practice	許永居 主任 嘉義基督教醫院 神經內科	盧相如 主任 高雄醫大附設醫院 神經內科
10:40-11:00	Coffee break		
11:00-11:30	Medication overuse headache	陳炳錕 院長 台中博智診所	陳彥宇 主任 彰化基督教醫院 神經內科
11:30-12:00	Neuroimaging in the diagnosis of headache disorders	楊富吉 主任 三軍總醫院 神經內科	陳威宏 主任 台北新光醫院 神經內科
12:00-13:00	Lunch (理監事會議)		
13:00-13:30	Migraine comorbidity: depression, anxiety and others	王署君 主任 台北榮總 神經內科	葉篤學 主任 台北醫大附設醫院 神經內科
13:30-15:00	Workshop 【Botulinum toxin in migraine treatment】- Introduction and Hands-On	王嚴鋒 秘書長 台灣頭痛學會	陳韋達 理事長 台灣頭痛學會
15:00-15:15	Discussion	王署君 主任 台北榮總 神經內科	
15:15-15:30	Coffee break		
15:30-17:00	筆試(西側包廂) / 術科(東側包廂)	王嚴鋒 秘書長 台灣頭痛學會	

1.本課程已申請台灣神經學學會教育學分。
2.報名資格：具神經科專科醫師或神經外科專科醫師身份。
3.檢附資料：【神經科】或【神經外科】專科醫師證書影本。
4.限額 100 名，額滿為止。(須完成線上報名、繳費及檢附資料才算報名完成)。
5.報名費用：**非會員 2000 元、會員 1500 元(皆含餐點)**。現場加入會員優待減免 500 元。
6.報名方式：

- 一律採線上報名：https://forms.gle/hUPpF4u2vDLBP6so7
- 參加者請於 110 年 4 月 6 日前完成報名、繳費及檢附資料

7.繳費方式：(劃撥者姓名須與報名者相同)

- 即日起至 110 年 4 月 6 日止。
- 於劃撥單通訊欄備註：110 年中區慢性偏頭痛診斷與治療訓練課程
- **郵政劃撥帳號：19941337，戶名：台灣頭痛學會**

8.訓練通過考試者，名單會公告於學會網頁及寄發合格證書，有效期限為 6 年。
9.歡迎大家加入台灣頭痛學會(入會費 1000 元，年會 1000 元/年)
聯絡人：何沛儒小姐 (02)28712121 ext 3248
台灣頭痛學會信箱：ths.lw@hotmail.com

2021

Headache evaluation and classification

楊鈞百 MD PhD

光田醫療社團法人光田綜合醫院
神經內科兼醫學研究部主任
睡眠中心兼靜脈雷射中心主任
弘光大學營養系 部定兼任副教授
美國史丹佛大學睡眠中心研究

2021.04.11

Diagnose of Headache

- ***History taking***
  - ***ICHD - 3 (International Classification of Headache Disorders, 3rd edition)***
- ***Neurological examinations***
- ***Brain Image or laboratory studies***

ICHD -3 (International Classification of Headache Disorders, 3rd edition) The latest version !!

第三版
國際頭痛疾病分類

Cephalalgia 2018; 38: 1–211

The International Classification of Headache Disorders 3rd edition (ICHD-III) 2018

Part 1: Primary headaches 頭痛本身即為一種疾病

Part 2: The secondary headache 頭痛只是其他病的症狀之一

Part 3: Painful cranial neuropathies, other facial pains and other headaches

絕大多數的頭痛是原發性頭痛 (90%)

Cephalalgia 2018; 38: 1- 211

Headache History Taking

***L*ocation:** *temple, ocular… unilateral or bilateral*

Q*uality: character (throbbing, tightness..); intensity (VAS)*

***Q*uantity:** *frequency; duration*

***O*nset:** *sudden, acute, subacute, chronic*

***P*recipitating/ *P*rovoking** *factors: head injury, 3C food ..*

***E*xaggerating** *factors: valsava maneuver, position related..*

***R*elieving factors:** *lying, standing..*

***A**ssociated symptoms: nausea/vomiting, photophobia..*

ICHD-3 Overview

Primary Headache

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders

Painful cranial neuropathies, other facial pains and other headaches

13. Painful cranial neuropathies and other facial pains
14. Other headache disorders

Secondary Headache

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder

Part I

The primary headache

原發性頭痛 The Primary Headache

1. 偏頭痛 Migraine	19
2. 緊縮型頭痛 Tension-type headache (TTH)	7
3. 三叉自律神經頭痛 Trigeminal autonomic cephalalgias	8
4. 其他原發性頭痛疾病 Other primary headache disorders	14

1. 偏頭痛 Migraine

1.1 無預兆偏頭痛 Migraine without aura
1.2 預兆偏頭痛 Migraine with aura
1.3 慢性偏頭痛 Chronic migraine
1.4 偏頭痛併發症 Complications of migraine
1.5 極可能偏頭痛 Probable migraine
1.6 可能與偏頭痛相關之陣發性症候群 Episodic syndromes that may be associated with migraine

偏頭痛

神經內科門診最常見的頭痛
(60-90%)

也是最令病人痛不欲生的頭痛

ICHD-3 1.1 Migraine without aura

A. ≧ 5 attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72

C. Headache has ≥2 of the following characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity

D. During headache ≥1 of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia

E. Not attributed to another disorder

Cephalalgia 2018

1.2 預兆偏頭痛 Migraine with aura

A. 至少有兩次發作符合基準B及C

B. 包括下列一或多項完全可逆的預兆症狀：
   1. 視覺
   2. 感覺
   3. 說話及/或語言
   4. 運動
   5. 腦幹
   6. 視網膜

C. 至少具下列六項特徵其中三項：
   1. 至少一種預兆症狀在 ≥ 5分鐘逐漸發展
   2. 兩種或兩種以上的預兆症狀接續發生
   3. 每一種個別的預兆症狀持續5-60分鐘
   4. 至少有一種預兆症狀是單側的
   5. 至少有一種預兆症狀是正向的
   6. 預兆會同時伴隨頭痛或於預兆後60分鐘內頭痛

D. 沒有其他更合適的ICHD-3診斷

1.2 預兆偏頭痛 Migraine with aura

1.2.1 典型預兆偏頭痛 Migraine with typical aura
  1.2.1.1 典型預兆頭痛 Typical aura with headache
  1.2.1.2 不伴隨頭痛之典型預兆 Typical aura without headache
1.2.2 腦幹預兆偏頭痛 Migraine with brainstem aura
1.2.3 偏癱偏頭痛 Hemiplegic migraine
  1.2.3.1 家族性偏癱偏頭痛 Familial hemiplegic migraine (FHM)
  1.2.3.2 散發性偏癱偏頭痛 Sporadic hemiplegic migraine (SHM)
1.2.4 視網膜偏頭痛 Retinal migraine

TABLE 1: Aura categories and subtypes of migraine with aura

Aura symptoms	Aura categories	Subtypes of migraine with aura
Visual	Typical aura	1.2.1 Migraine with typical aura
Sensory		
Speech/language		
Brainstem	Brainstem aura	1.2.2 Migraine with brainstem aura
Motor	Motor aura	1.2.3 Hemiplegic migraine
Retinal	Retinal aura	1.2.4 Retinal migraine

Modern Day Management of Headache: Questions and Answers. Jaypee Brothers Medical Publishers, India 2017

1.2.1 典型預兆偏頭痛 Migraine with typical aura

A.發作符合1.2*預兆偏頭痛*的診斷基準及以下基準B
B.預兆符合以下兩項：
1. 完全可逆的視覺、感覺及/或說話/語言症狀
2. 沒有運動、腦幹或視網膜症狀

腦幹預兆 Brainstem aura

預兆符合以下兩項：

1. 至少包括下列兩項完全可逆的腦幹症狀：
    a)構音障礙
    b)眩暈
    c)耳鳴
    d)聽力低下 (hypacusia)
    e)複視
    f)非歸因於感覺障礙之共濟失調 (ataxia)
    g)意識障礙 (GCS ≤ 13)
2. 沒有運動和視網膜症狀

1.2.3 偏癱偏頭痛 Hemiplegic migraine

A.發作符合1.2*預兆偏頭痛*的診斷基準及以下基準B

B.預兆包含以下兩項：

1. 完全可逆的肢體無力
2. 完全可逆的視覺、感覺、及/或說話/語言症狀

1.2.3 偏癱偏頭痛 Hemiplegic migraine

1.2.3.1 家族性偏癱偏頭痛 Familial hemiplegic migraine (FHM)

CACNA1A，ATP1A2或SCN1A基因的致病突變

1.2.3.2 散發性偏癱偏頭痛 Sporadic hemiplegic migraine (SHM)

1.2.4 視網膜偏頭痛 Retinal migraine

A.發作符合1.2*預兆偏頭痛*的診斷基準及以下基準B
B.預兆具有下列兩項特徵：
1. 包括完全可逆之單眼正向及/或負向視覺症狀 (如：閃光、暗點或失明)，發作時經由下列一項或兩項證實：
   a)臨床視野檢查
   b)(在清楚的指示下) 由病人描繪發作時的單眼視野缺陷
2. 至少具下列兩項特徵：
   a)在≥5分鐘逐漸發展
   b)症狀持續5-60分鐘
   c)同時伴隨頭痛或於預兆後60分鐘內頭痛

C.沒有其他更合適的ICHD-3診斷，且排除其他造成黑矇症 (amaurosis fugax) 的原因

1.3 慢性偏頭痛 Chronic migraine

A.頭痛 (可以類偏頭痛 (migraine-like) 及/或類緊縮型 (tension-type-like)) 發作每月 ≥ 15天，已 > 3個月，且符合基準B及C

B.發生於已經有至少五次發作符合基準1.1*無預兆偏頭痛*B-D項及/或1.2*預兆偏頭痛* B及C項的病人

C.發作每月 ≥ 8天，已 > 3個月，且符合下列之一：

1. 基準1.1*無預兆偏頭痛* C及D項
2. 基準1.2*預兆偏頭痛* B及C項
3. 開始發作時病人相信是偏頭痛發作，而且使用翠普登 (triptan) 或麥角鹼藥物 (ergot derivative) 可達到緩解

D. 沒有其他更合適的ICHD-3診斷

1.4 偏頭痛併發症 Complications of migraine

1.4.1 偏頭痛重積狀態 Status migrainosus
1.4.2 無梗塞之持續預兆 Persistent aura without infarction
1.4.3 偏頭痛腦梗塞 Migrainous infarction
1.4.4 偏頭痛預兆引發之癲癇發作 Migraine aura-triggered seizure

1.4.1 偏頭痛重積狀態 Status migrainosus

不間斷持續 > 72 小時
疼痛及/或其他相關症狀使人失能
藥物或睡眠而頭痛緩解可接受的時間最長12小時

1.4.3 偏頭痛腦梗塞
Migrainous infarction

一或多種預兆症狀持續 > 60 分鐘
神經影像證實在相關區域出現缺血性腦梗塞

1.5 極可能偏頭痛 Probable migraine

尚缺其中任何一項，就完全符合 1.1 無預兆偏頭痛基準 A-D 或是 1.2 預兆偏頭痛基準 A-C

- 在下頭痛診斷時，如果發作同時符合緊縮型頭痛和極可能偏頭痛，則登錄前者，因為確定診斷優先於極可能診斷。
- 如果病人原先已被診斷為偏頭痛，那問題只在於是否將之列入發作次數計算 (例如：在藥物試驗時)，發作符合 1.5 極可能偏頭痛的基準應列為偏頭痛發作。

附錄（Appendix)

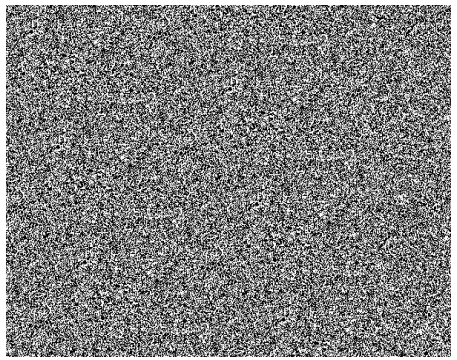
附錄的主要目的，是提出研究用的診斷基準，以供迄今未經研究充分驗證的一些新興疾病實體所用。根據分類委員會專家的經驗以及品質不一的已發表文獻，顯示這些診斷實體有許多是真實的，但須更好的科學證據才能正式認可。因此，有些附錄中的疾患可能在下一版中移動至分類的本文內。

在一些地方，附錄提供了對應分類本文的 替代用診斷基準。同樣的，臨床經驗和一定數量的文獻證據雖顯示替代基準可能較佳，但委員會認為證據尚不足以改變主分類。

列於先前版本 ICHD 中的診斷實體，若尚未有充分的證據出現，列於附錄是將它 刪除的第一步。

A1.4.6 視雪 Visual snow

A.動態的、持續的微細小點散布整個視野，持續 > 3個月
B.附加視覺症狀至少有以下四項型態其中兩項：
    1. 持續後像 (palinopsia)
    2. 內視現象增強 (entoptic phenomenon)
    3. 畏光
    4. 夜間視力欠佳 (夜盲，nyctalopia)
C.症狀和典型視覺預兆症狀不一致
D.症狀無法歸因於其他更合適的疾患



A1.6.6 前庭偏頭痛 Vestibular migraine

A. 至少有五次發作符合基準C及D
B. 現在或過去有符合1.1*無預兆偏頭痛*或1.2*預兆偏頭痛*的病史
C. 中或重度前庭症狀，持續五分鐘到72小時
D. 至少一半的發作會合併以下三項偏頭痛特徵中至少一項：
    1. 頭痛，至少具下列四項特徵其中兩項：
        a) 單側
        b) 搏動性
        c) 疼痛程度中或重度
        d) 日常活動會使頭痛加劇
    2. 畏光及怕吵
    3. 視覺預兆
E. 沒有其他更合適的ICHD-3或其他前庭疾患的診斷

2. Tension-type headache (TTH)
緊縮型頭痛

2.1 不常發陣發性緊縮型頭痛
Infrequent episodic tension-type headache
2.2 經常陣發性緊縮型頭痛
Frequent episodic tension-type headache
2.3 慢性緊縮型頭痛 Chronic tension-type headache
2.4 極可能緊縮型頭痛 Probable tension-type headache

Infrequent ETTH (<1 day/month) → frequent ETTH (1-14 days/month) → CTTH (≥ 15 days/month)

With or without pericranial tenderness

緊縮型頭痛

C. 至少具下列四項特徵其中兩項：
   1. 雙側
   2. 壓迫或緊縮性 (非搏動性)
   3. 疼痛程度輕或中度
   4. 不因日常活動如走路或爬樓梯而加劇

D. 符合下列兩項：
   1. 無噁心或嘔吐
   2. 畏光或怕吵最多只有其中一項

偏頭痛

C. 頭痛至少具下列四項特徵其中兩項：
   1. 單側
   2. 搏動性
   3. 疼痛程度中或重度
   4. 日常活動會使頭痛加劇或避免此類活動（如走路或爬樓梯）

D. 當頭痛發作時至少有下列一項：
   1. 噁心及/或嘔吐
   2. 畏光及怕吵

Tension-type headache is defined more by what it is not, more than what it is.

Curr Pain Headache Rep. 2009;13:484-94

3.Trigeminal autonomic cephalalgias (TACs)

三叉自律神經頭痛

3.1 Cluster headache 叢發性頭痛

3.2 Paroxysmal hemicrania 發作性半邊頭痛

3.3 Short-lasting unilateral neuralgiform headache attacks

(SUNA & SUNCT) 短暫單側神經痛性頭痛發作

3.4 Hemicrania continua 持續性半邊頭痛

3.5 Probable trigeminal autonomic cephalalgia

極可能三叉自律神經頭痛

Common features of TACs

Unilateral headache

Distribution of the **trigeminal** nerve (**orbit, supraorbital and/or temporal regions**)

Prominent **cranial parasympathetic autonomic features**, lateralized and ipsilateral*

1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead and facial sweating
5. Miosis and/or ptosis

*Absent in only 3% of cases

Cluster attacks

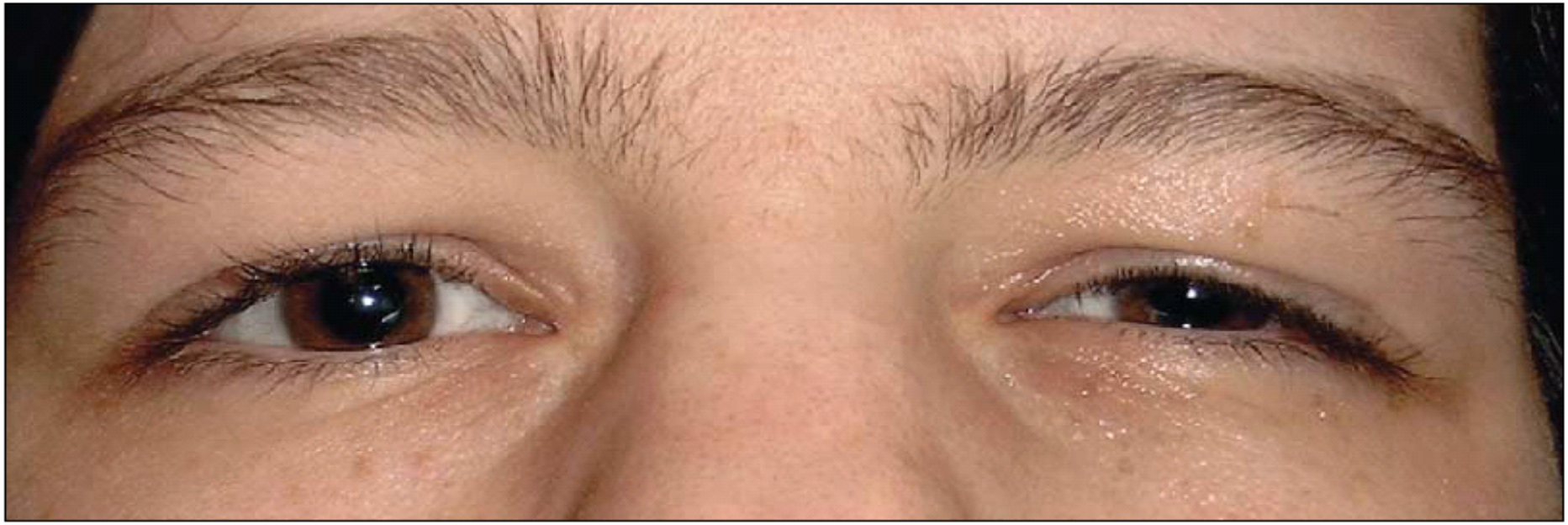


Figure 1: **Patient soon after a left-sided cluster headache attack**
Note the Horner syndrome ipsilateral to the headache and increased facial sweating exclusively around the left eye.

May A. Lancet 2005

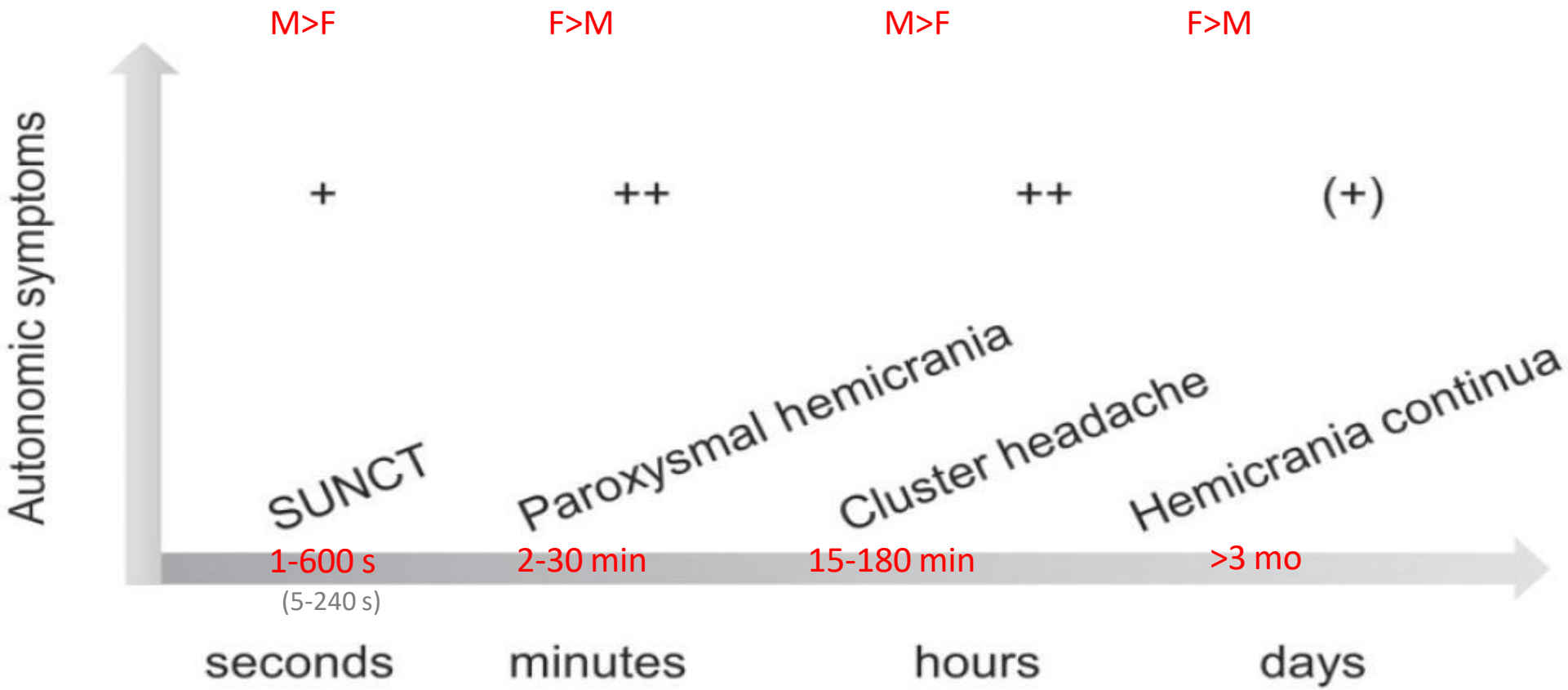
3. Trigeminal autonomic cephalalgias

1. Cluster headache
2. Paroxysmal hemicrania
3. Short-lasting unilateral neuralgiform headache attacks (SUNCT)

} (<4 hrs)

4. Hemicrania continua **(>4 hrs)**
5. Probable TACs

Differential diagnosis of TACs



Hemicrania => female + indomethacin

Headache 2013;53:1470-1478

Secondary trigeminal autonomic cephalalgia

- Sellar region tumor
- Maxillary sinus foreign body
- Facial trauma
- Orbitosphenoidal aspergillosis
- Orbital myositis
- Head or neck injury
- High cervical meningioma

- Cervical or intracranial artery dissection
- Pseudoaneurysm of intracavernous carotid artery
- Aneurysms (anterior communicating artery, Basilar artery, Carotid artery)
- Arteriovenous malformation (MCA territory, Occipital lobe…)
- Unilateral cervical cord infarction
- Lateral medullary infarction

Brain MRI is a must!

Cluster headache

A: At least 5 attacks fulfilling criteria B-D

B: Severe or very severe unilateral orbital, supraorbital and or temporal pain lasting 15-180 min if untreated

C: Headache is accompanied by ≥ 1 of the following:

1. ipsilateral conjunctival injection and /or lacrimation
2. ipsilateral nasal congestion and /or rhinorrhea
3. ipsilateral eyelid edema
4. ipsilateral forehead and facial sweating
5. ipsilateral miosis and /or ptosis
6. a sense of restlessness or agitation

D: attack have a frequency from $\frac{1}{2}$ d to 8/d

E; not attributed to another disorder

3.1 Cluster headache

3.1.1 Episodic cluster headache 陣發叢發性頭痛 G44.01

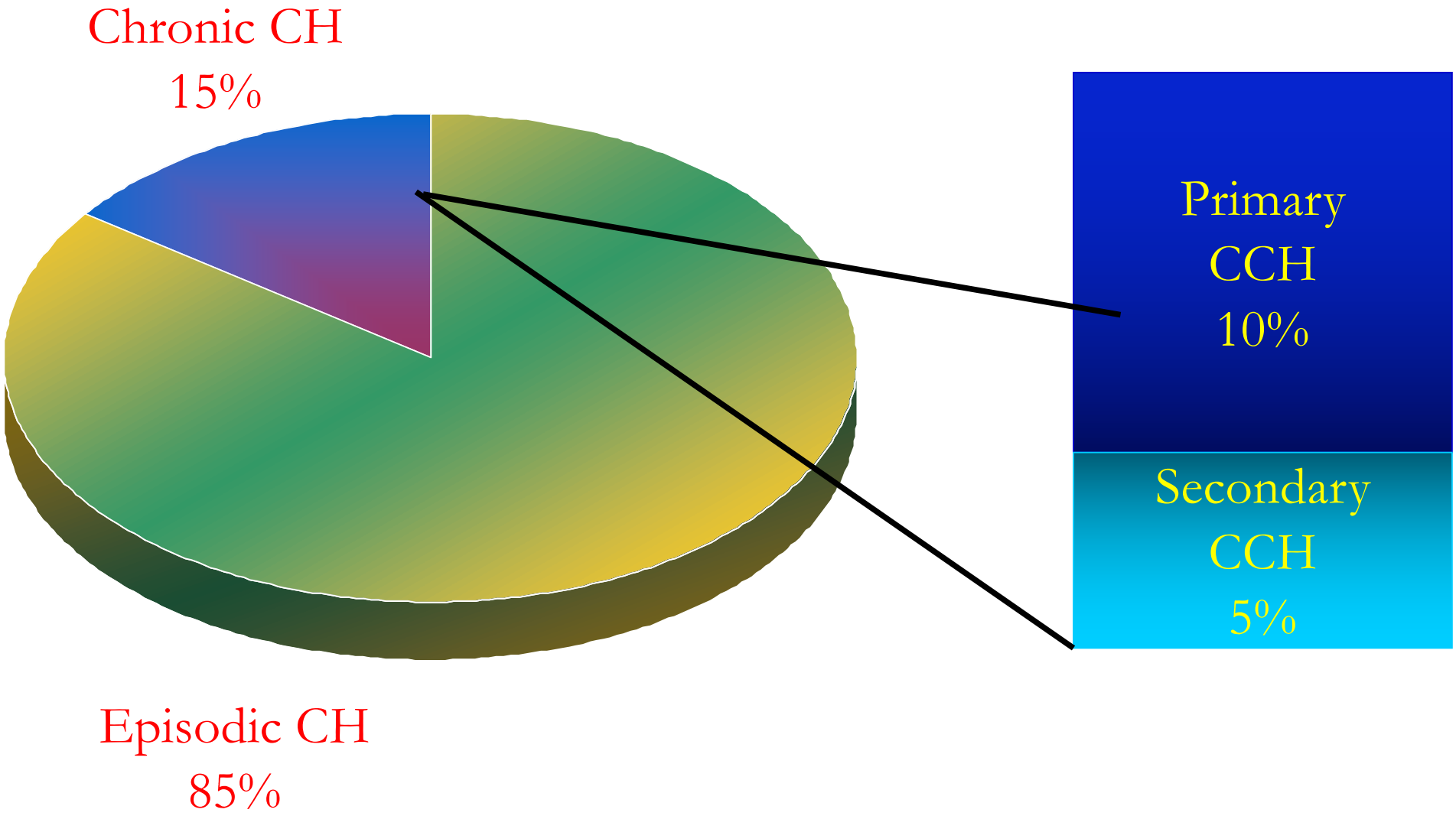
A. Attacks fulfilling criteria for 3.1 Cluster headache and occurring in bouts (cluster periods)

B. At least 2 cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months

3.1.2 Chronic cluster headache 慢性叢發性頭痛 G44.02

A. Attacks fulfilling criteria for 3.1 Cluster headache and criterion B below

B. Occurring without a remission period, or with remissions lasting <3 months, for at least one year.



Cephalalgia, 2000;20:787-803

3.3 Short-lasting unilateral neuralgiform headache attacks G44.05

短暫單側神經痛性頭痛發作

A. At least 20 attacks fulfilling criteria B–D

B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1–600 seconds and occurring as single stabs, series of stabs or in a saw-tooth pattern

C. At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain:

a) conjunctival injection and/or lacrimation

b) nasal congestion and/or rhinorrhoea

c) eyelid edema

d) forehead and facial sweating

e) miosis and/or ptosis

D. Occurring with a frequency of at least one a day

E. Not better accounted for by another ICHD-3 diagnosis.

3.2 Paroxysmal hemicrania G44.03

A. At least 20 attacks fulfilling criteria B-E

B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes

C. Either or both of the following:

1. at least one of the following symptoms or signs, ipsilateral to the headache:
    a) conjunctival injection and/or lacrimation
    b) nasal congestion and/or rhinorrhoea
    c) eyelid edema
    d) forehead and facial sweating
    e) miosis and/or ptosis
2. a sense of restlessness or agitation

D. Occurring with a frequency of >5 per days

E. Prevented absolutely by therapeutic doses of indomethacin

F. Not better accounted for by another ICHD-3 diagnosis

*During part, but less than half, of the active time-course of 3.2 Paroxysmal hemicrania, attacks may be less frequent.

*In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100–200 mg. Smaller maintenance doses are often employed.

3.4 Hemicrania continua G44.51

A. Unilateral headache fulfilling criteria B–D

B. Present for > 3 months, with exacerbations of moderate or greater intensity

C. Either or both of the following:

1. at least one of the following symptoms or signs, ipsilateral to the headache:
   a) conjunctival injection and/or lacrimation
   b) nasal congestion and/or rhinorrhea
   c) eyelid edema
   d) forehead and facial sweating
   e) miosis and/or ptosis
2. a sense of restlessness or agitation, or aggravation of the pain by movement

D. Responds absolutely to therapeutic doses of indomethacin

E. Not better accounted for by another ICHD-3 diagnosis.

4. Other primary headache disorders

1. Primary cough headache 原發性咳嗽頭痛
2. Primary exercise headache 原發性運動頭痛
3. Primary headache associated with sexual activity 原發性性行為相關之頭痛
4. Primary thunderclap headache 原發性雷擊頭痛
5. Cold-stimulus headache 冷刺激頭痛
6. External pressure headache 外在壓力性頭痛
7. Primary stabbing headache 原發性刺戳性頭痛
8. Nummular headache 錢幣狀頭痛
   Hypnic headache 睡眠頭痛
9. New daily persistent headache (NDPH) 新發生每日持續性頭痛

Other primary headache disorders

Physical exertion

Valsalva-induced headaches

- 4.1 Primary cough headache
- 4.2 Primary exercise headache
- 4.3 Primary headache associated with sexual activity
- 4.4 Primary thunderclap headache

Direct physical stimuli

- 4.5 Cold-stimulus headache
- 4.6 External-pressure headache

Epicranial headaches

- **4.7 Primary stabbing headache**
- 4.8 Nummular Headache
- A4.11 Epicrania Fugax

Others

- **4.9 Hypnic headache**
- 4.10 New daily persistent headache (NDPH)

Indomethacin-responsive headaches

- ICHD-3

(1) Trigeminal autonomic cephalgias: TAC

- Paroxysmal hemicrania (3.2)
- Hemicrania continua (3.4)

(2) Other primary headaches

-Primary cough headache (4.1)
-Primary exercise headache (4.2)
-primary headache associated with sexual activity (4.3)
-Primary stabbing headache (4.7)

-Hypnic headache (4.9)

Curr Neurol Neurosci Rep (2015) 15:516

Diagnostic indomethacin trial

- Starting from 25mg tid
- Titrate every 3 days, with additional 25mg
  - 25mg tid →for 3 days, if no response →
  - 50mg tid →for 3 days, if no response →
  - 75mg tid →if no response → fail
- Be aware of the possible adverse effect!

  e.g. GI injury, renal dysfunction, exacerbation of congestive heart failure, bleeding from PLT inhibition…

Complete resolution of the headache is usually prompt, occurring within one to two days of initiating the effective dose

非急性頭痛之神經影像檢查準則

台灣頭痛學會治療準則小組

中文摘要

本小組針對非急性頭痛患者安排神經影像檢查之適應症，以實證醫學的方式，評估過去文獻的品質、證據等級並參考歐美國家的相關準則，歷經數次討論與意見整合，提出共識。

非急性且反覆發作的偏頭痛或緊縮型頭痛，若頭痛特徵近期內無改變，且神經學檢查爲正常時，影像檢查並非必要。非急性頭痛患者且有異常的神經學檢查，建議應接受影像檢查。對於被診斷爲叢發性頭痛且從未接受過神經影像檢查或是有非典型症狀的叢發性頭痛的病人，應考慮做影像檢查。對於有咳嗽頭痛、運動頭痛(出力頭痛)及與性行爲相關頭痛的病人，建議應接受影像檢查。

雖然磁振造影的敏感度優於電腦斷層，但目前無足夠證據來建議應選擇磁振造影或電腦斷層，醫師仍應根據病患個別的病況來判斷。

4.7 Primary stabbing headache

原發性刺戳性頭痛

ICHD-3 diagnostic criteria 4.7

A. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D

B. Each stab lasts for up to a few seconds

C. Stabs recur with irregular frequency, from one to many per day

D. No cranial autonomic symptoms

E. Not better accounted for by another ICHD-III diagnosis

No autonomic symptoms (D/D SUNCT)

Single vs. multiple

Prevalence of 35.2% (not rare!); common in migraineurs

80% of stabs ≤ 3 secs; rarely 10-120 secs

Female preponderance ; mean AAO: 28 years

May move, if fixed→ consider 2nd

Treatment: Indomethacin, melatonin, celecoxib, nifedipine, and gabapentin

Reassurance about their benign nature

4.9 Hypnic Headache (ICHD-3)

A. Recurrent headache attacks fulfilling criteria B-E

B. Developing only during sleep, and causing wakening

C. Occurring on ≧10 days per month for >3 months

D. Lasting ≧15 minutes and for up to 4 hours after waking

E. No cranial autonomic symptoms or restlessness

F. Not better accounted for by another ICHD-III diagnosis.

- Usually mild to moderate, 20% severe pain , 2/3 bilateral
- Most cases are chronic
- Both REM & non-REM
- D/D: drug withdrawal, nocturnal hypertension, sleep apnea, brain tumors, temporal arteritis, primary headaches (migraine, cluster headaches and chronic paroxysmal hemicrania…)
- Treatment: Caffeine, **lithium**, melatonin, indomethacin

Manni R et al. Neurology 2004; Liang JF et al. Cephalalgia 2008; Donnet A et al. Cephalalgia 2009, Holle D et al. Cephalalgia 2010, 2011 & Ann Neurol 2011

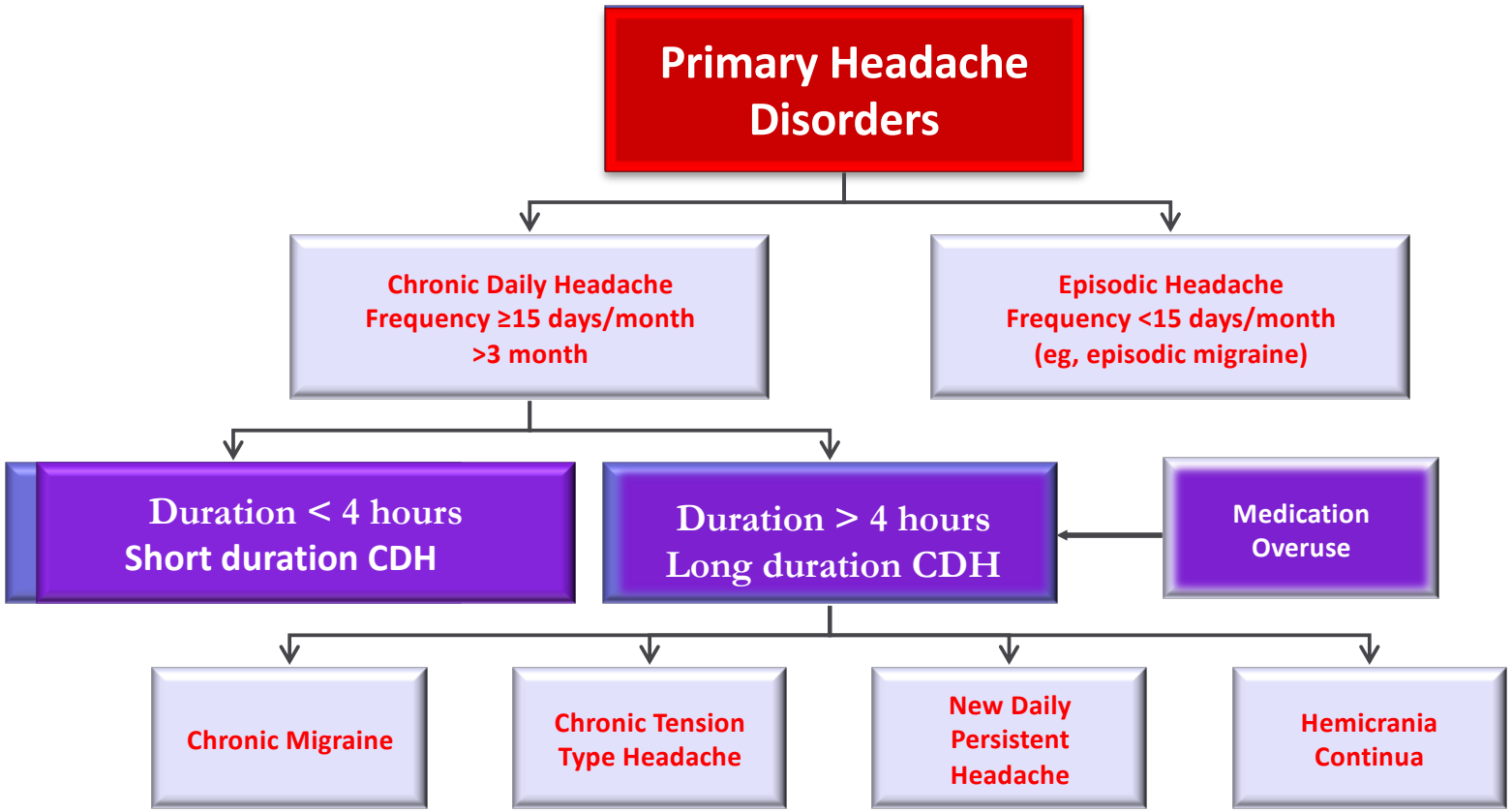
4.10 New daily persistent headache (NDPH)

新發生每日持續性頭痛

A. Persistent headache fulfilling criteria B and C
B. Distinct and clearly-remembered onset, with pain becoming continuous and unremitting within 24 hours
C. Present for >3 months
D. Not better accounted for by another ICHD-3 diagnosis.

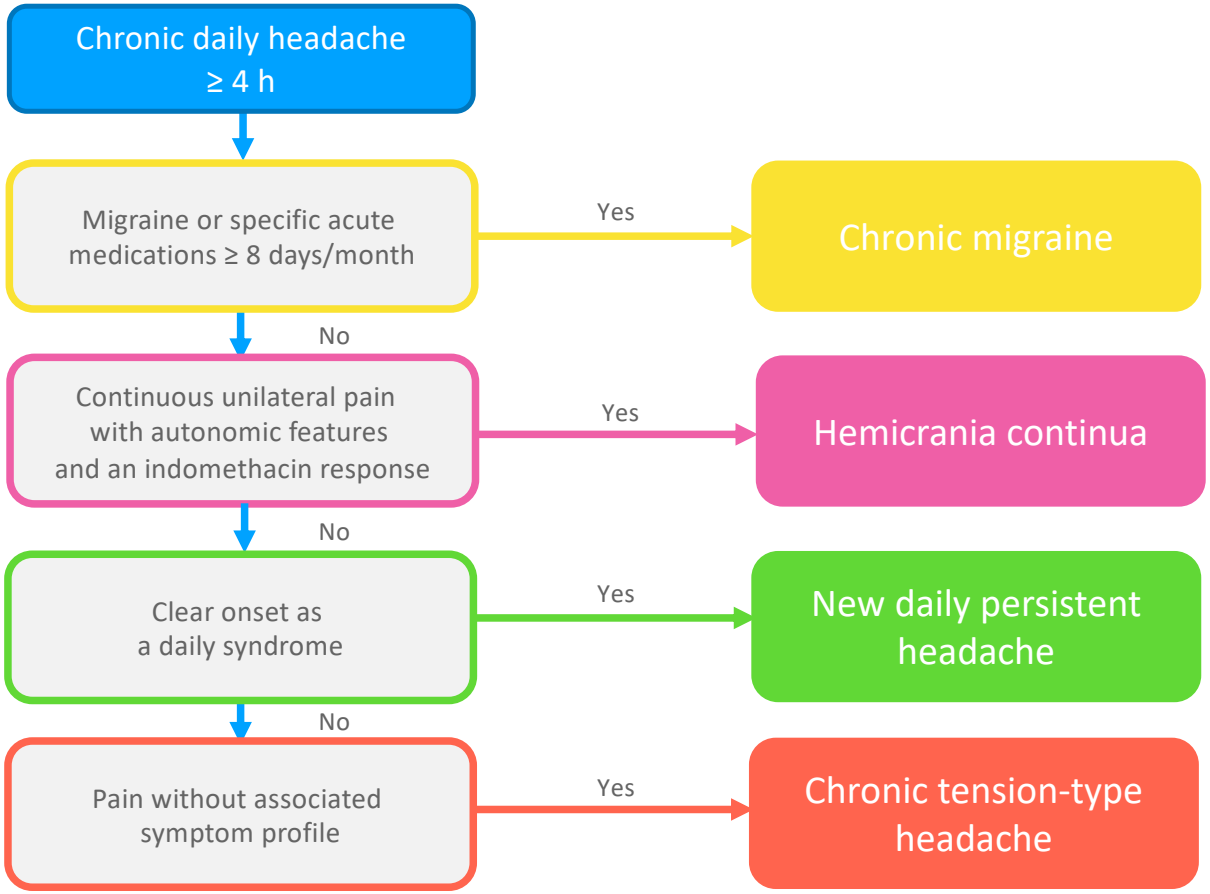
- Prevalence between 0.03%-0.1%
- Majority (82%) were able to recall the day of onset
- Commonly seen in the fourth decade although any age may be affected
- The exact etiology and pathophysiology of primary NDPH remains unclear
- Refractory to currently available treatments particularly one with pronounced migrainous features

Primary Headache Disorders: Frequency Classification



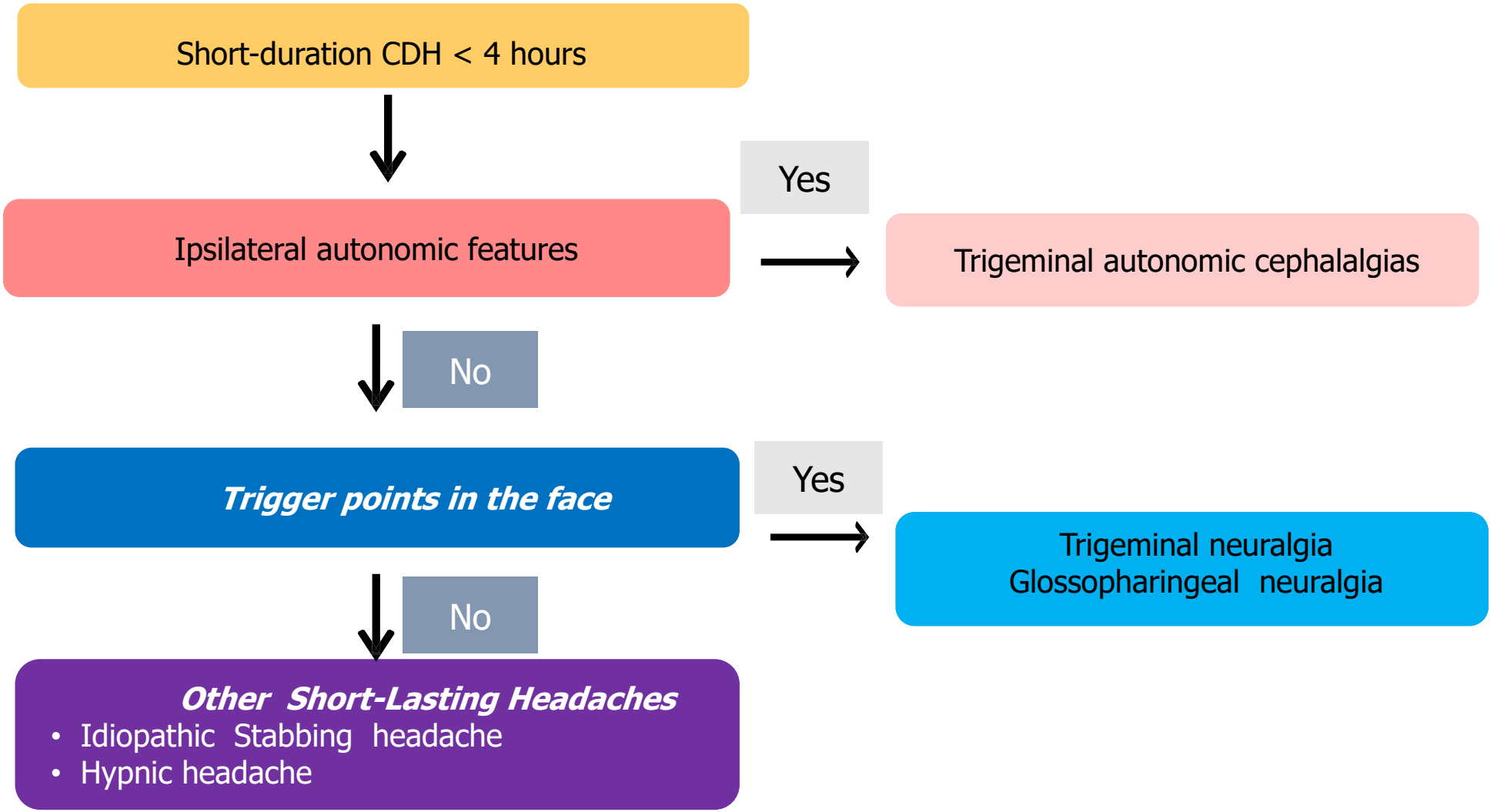
Silberstein S et al. Neurology 1996;47;871-875

Long duration of chronic daily headache



Adapted from Bigal & Lipton. J Headache Pain 2007;8:263–72.

Short duration of chronic daily headache



Part II

The Secondary headache

Headache Diagnosis Algorithm and treatment in clinical practice

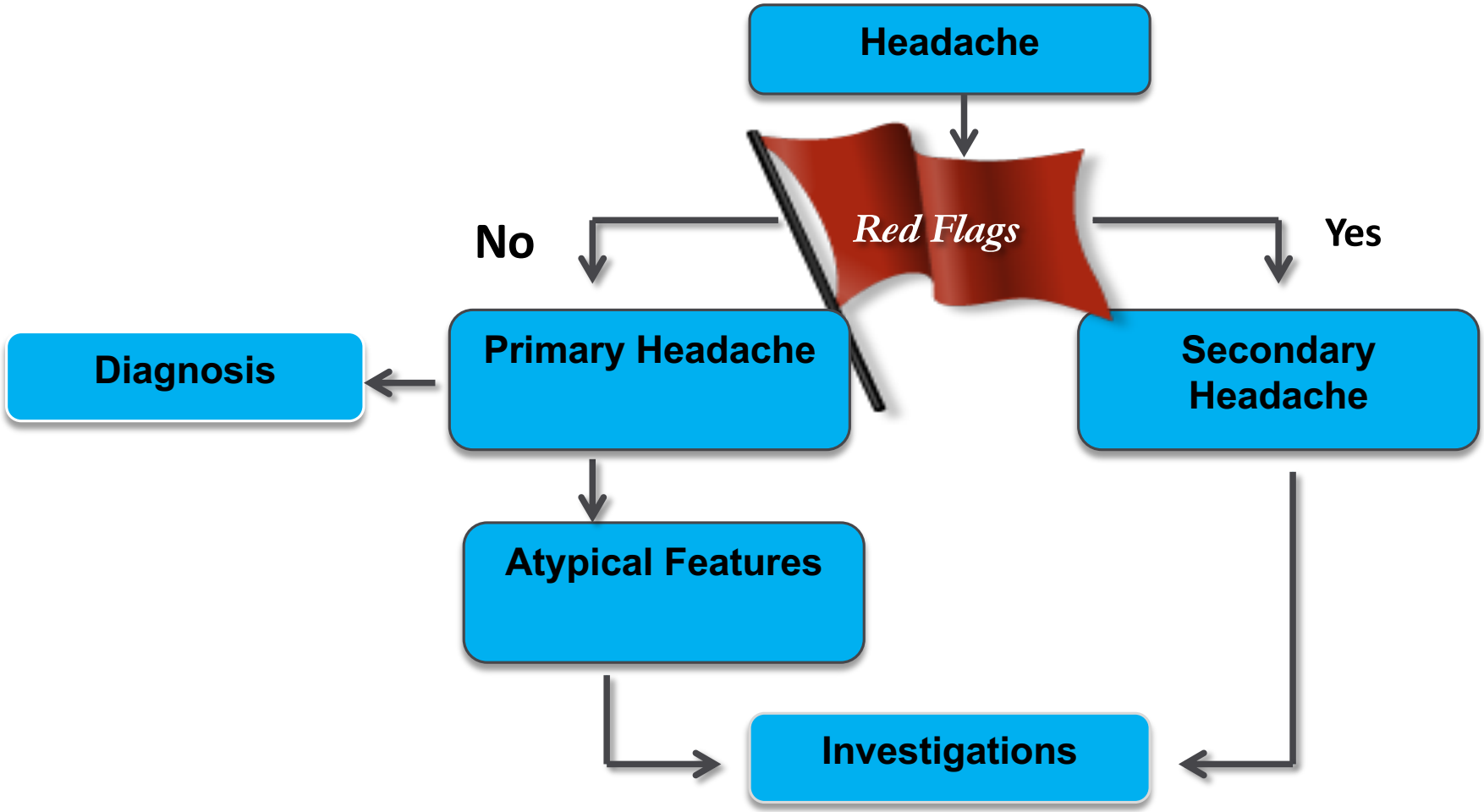
Exclude secondary headache

Make a correct Diagnosis (primary headache)

Optimize the acute treatment

Discuss the need for prevention

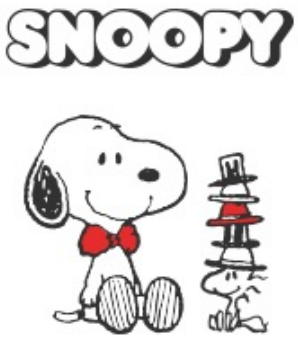
Distinguish Primary from Secondary Headache Disorders



How could we rule out secondary headache?

Red-flags of headache?

SNOOP[4]?



Red Flags-SNOOP 4

	Clinical feature(s)	Need to exclude
S	Systemic symptoms: fever,chills,myalgia,weight loss	Metastasis, infection
N	Neurological symptoms or deficits	Stroke, mass lesion, encephalitis
O	Older age at onset (>50years)	Temporal arteritis, glaucoma, mass lesion
O	Onset, thunderclap headache onset	SAH, ICH, artery dissection, RCVs, venous thrombosis
P	Papilledema	Raised intracranial pressure
P	Positional	Intracranial hypotension
P	Precipitated by Valsalva maneuvre or exertion	Raised intracranial pressure
P	Progressive headache or substantial pattern change	Any secondary cause

Dodick DW. Adv Stud Med. 2003; 3:S550-S555.

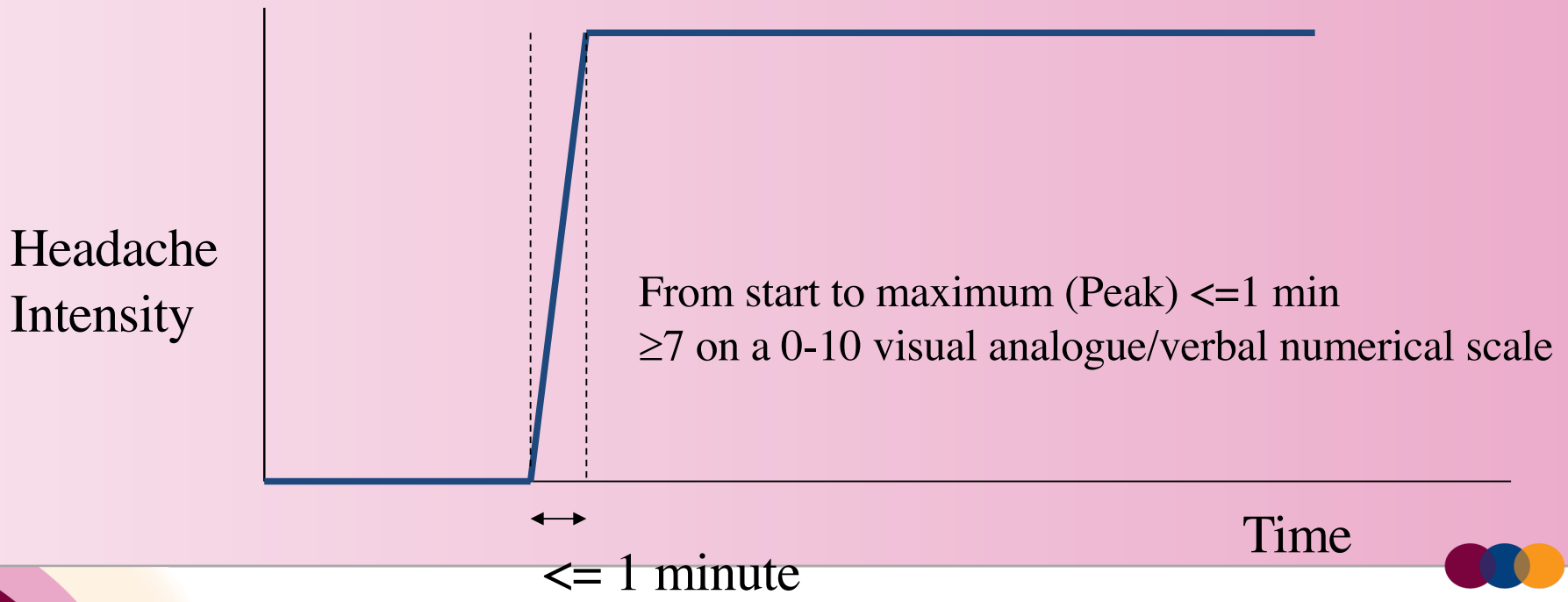
Red-flags of headache

- Who
  - Onset age >50
- When
  - Onset sudden <1 min
  - Progressive non-remitting
- How
  - First ever severe headache
  - Pattern/severity change

Red-flags of headache

- What
  - Associated symptoms:
    - Drowsiness, confusion, memory loss
    - Chronic malaise, myalgia, arthralgia
    - Fever
    - Progressive visual disturbances
    - Weakness, clumsiness, loss of balance
- Why
  - Precipitated by valsava maneuver or exertion
  - Precipitated by posture change

Thunderclap headache



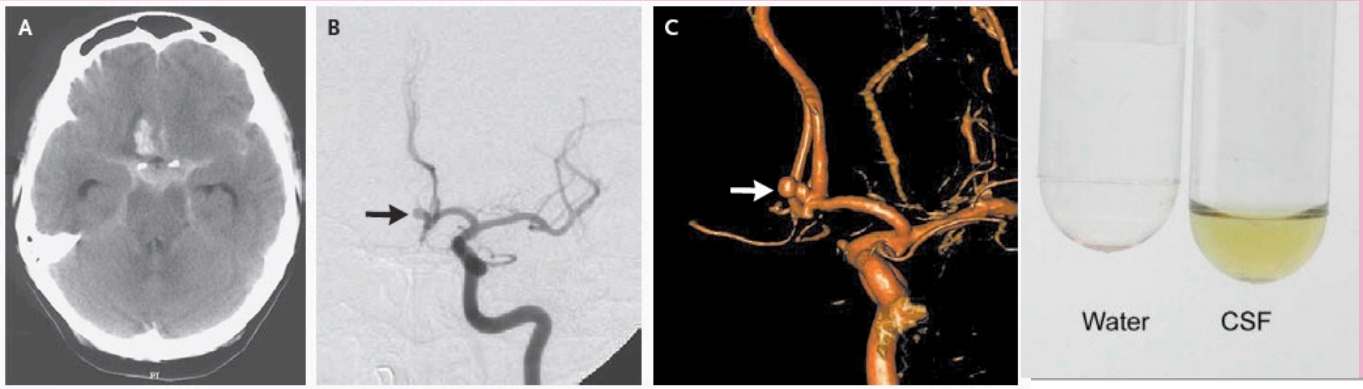
Causes of Thunderclap Headache

(onset to peak < 1 min)

Primary	Secondary	
	Vascular disorders	***Nonvascular disorders***
Migraine, crash Cluster HA Primary TCH Exercise headache Cough headache Sexual headache	SAH RCVS Arterial dissection Intracerebral hemorrhage Veno-sinus thrombosis Unruptured aneurysm**?** Hypertensive encephalopathy Pituitary apoplexia Myocardial infarction	3rd ventricle cysts/tumors Spontaneous intracranial hypotension Sinusitis Meningitis/encephalitis Erve virus Greater occipital neuralgia

Subarachnoid hemorrhage (SAH)

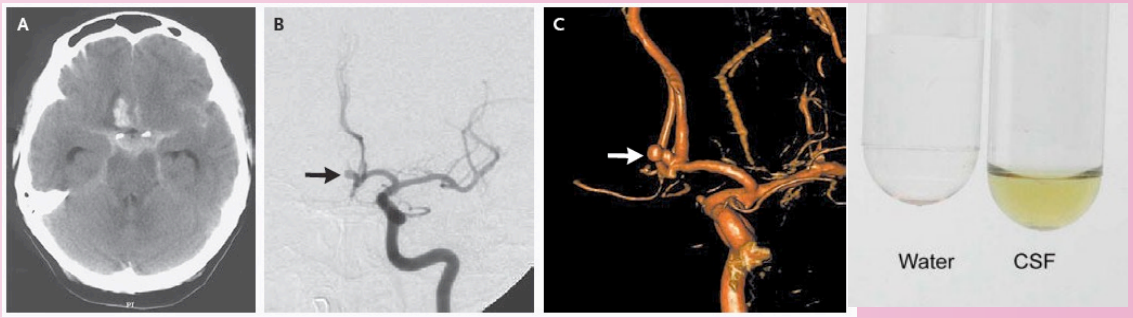
- 11-33% of thunderclap headaches are due to a SAH
- 74% of SAH presented with sudden severe headache
- First attack of TCH → SAH should be considered first
- If brain CT performed within 6 hours and data is normal, roughly 1/1000 is SAH
- LP should be performed for highly suspected SAH if brain CT is negative



Lancet 1994; 344: 590-3; N Engl J Med. 2000;342:29-36; N Engl J Med 2006;354:387-96.

Lumbar puncture

- ✓ Xanthochromia (RBC lysis)
- ✓ Timing; 12 hours - 2 weeks
- ✓ A need for CSF spectrophotometry or Visual inspection enough?
- ✓ Bloody, 3 tube test
- ✓ CTA ?



CTA: 2016 AAEM guideline

Recommendation (level B)

- ✓ CTA may be an appropriate alternative in those patients at higher risk for SAH after a negative NCCT and in those situations where a diagnostic LP is either refused by the patient or the results of the LP are equivocal
- ✓ CTA or Angiography is not necessary in patients with negative CT and LP

6.7.3 歸因於可逆性腦血管收縮症候群(RCVS)之頭痛

診斷基準:

A. 任何新發生的頭痛符合基準 C
B. 診斷為可逆性腦血管收縮症候群(RCVS)
C. 至少符合下列 1 項佐證其因果關係:
1. 頭痛,有/無(臨床)局部缺損及/或癲癇,導致血管造影呈現串珠狀表現與診斷為可逆性腦血管收縮症候群。
2. 頭痛至少符合下列 1 項特徵:
a) 1 個月內反覆發生,且雷擊式發病
b) 可由性行為、用力、Valsalva 氏操作、情緒、泡澡及/或淋浴所誘發

3. 發作>1 個月後無明顯、新頭痛發生

D. 沒有其他更合適的 ICHD-3 診斷,且已經由適當診察排除動脈瘤蜘蛛網膜下出血

Demonstration of RCVs

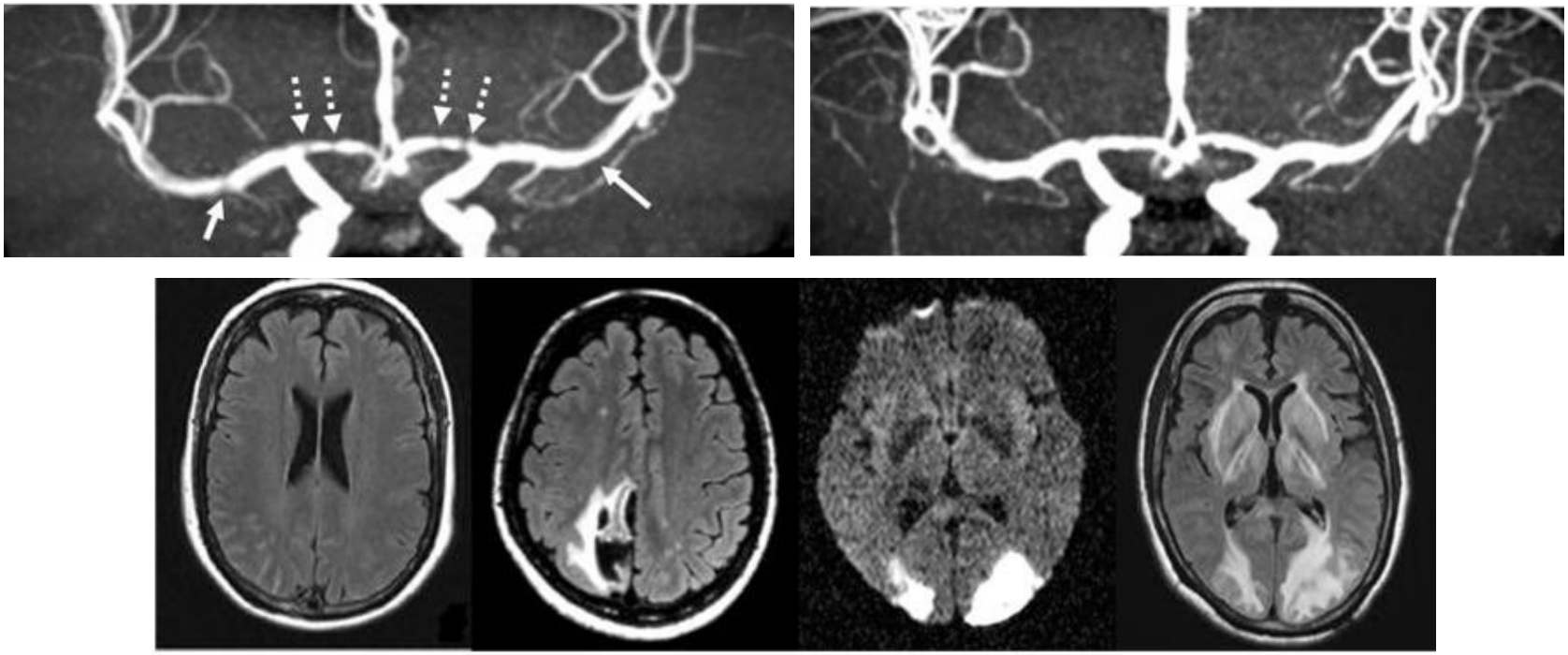
1.MRA

2. CT angiography (CTA)

3. Conventional Angiography: not recommended (invasive and 9% had transient neurological deficits)

4. Transcranial Color-coded Doppler study (TCCs)

RCVS and complications



cSAH 30-34%

ICH 12-20%

Ischemic stroke 8-39%

PRES 9-38%

原發性雷擊頭痛

A. 嚴重頭疼痛符合基準B及C

B. 下列兩項特徵皆符合：

1. 突發，＜1分鐘便可達到最嚴重強度
2. 持續1小時至10天

C. 接下來的幾個星期或幾個月並無規律的復發

D. 非歸因於其它疾患

Primary thunderclap headache/RCVs 的治療

常常是 self-limited

可能有復發或反覆發作(recurrent attack)

可能合併有腦血管收縮(vasospasm)

Nimodipine 可能可減緩症狀

Lu, S.R., et al. Neurology 2004;62:1414-6.

Chen, S.P., et al. Neurology 2006;67:2164-9.

歸因於腦脊髓液低壓之頭痛

A. 任何頭痛 (註 1) 符合基準 C

B. 符合下列一項或兩項:

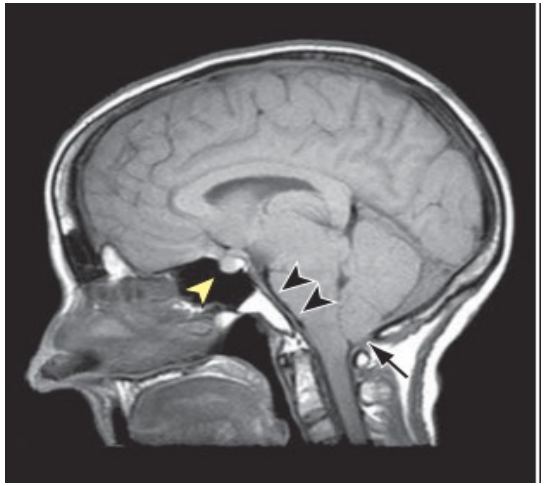
1. 腦脊髓液低壓 (< 60 mm CSF)

2. 影像學證實有腦脊髓液滲漏 (註 2)

C. 頭痛發生在時序上與腦脊髓液低壓或腦脊髓液滲漏相關,或導致其診斷 (註 3)

D. 沒有其他更合適的 ICHD-3 診斷

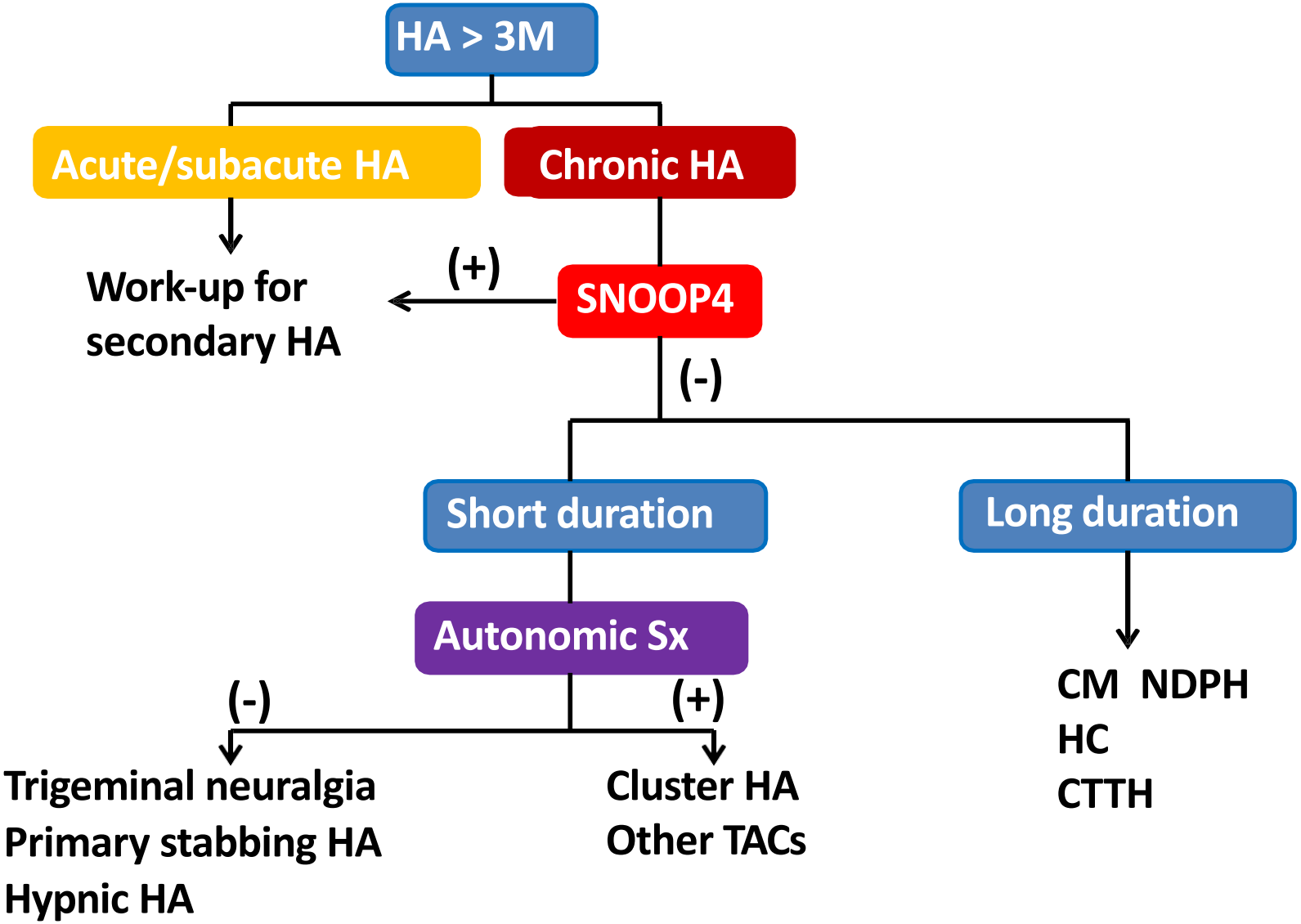
Brain MRI 有腦脊髓液低壓證據



- Subdural fluid collections (50%)
- Enhancement of the pachymeninges (70%)
- Engorgement of cerebral venous sinuses
- Pituitary enlargement
- "Sagging" of the brain, cerebellar tonsillar herniation (>4.3mm) and descent of the brainstem

But, 20% pt had negative MRI findings, including absence of pachymeningeal enhancement.

JAMA. 2006;295:2286-2296


HA > 3M
Acute/subacute HA
Chronic HA
Work-up for secondary HA
(+)
SNOOP4
(-)
Short duration
Long duration
Autonomic Sx
(-)
(+)
CM NDPH
HC
CTTH
Trigeminal neuralgia
Primary stabbing HA
Hypnic HA
Cluster HA
Other TACs

Thanks for your attention

歡迎加入台灣頭痛學會

台灣頭痛學會
Taiwan Headache Society

Diagnosis and treatment Chronic Migraine

活水神經內科診所
黃子洲

“Chronic” in ICHD-3

1. **Chronic** migraine and **chronic** TTH

   → frequent

2. **Chronic** cluster headache

   → without attack-free periods

3. **Chronic** secondary headaches

   → persists more than three months after the causative disease

4. **Persistent** secondary headaches

   → persists more than three months even the causative disease resolves

Cephalalgia. 2018;38:1-211

1.1 Migraine without aura

A. At least five attacks fulfilling criteria B–D

B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

U 1. unilateral location

P 2. pulsating quality

M 3. moderate or severe pain intensity

A 4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:

N噁 1. nausea and/or vomiting

P怕 2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

1.2 Migraine with aura

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least three of the following six characteristics:

1. at least one aura symptom spreads gradually over ≥ 5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5–60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis.

1.3 Chronic migraine

A. Headache (migraine-like or tension-type-like) on ≧ 15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On ≧8 days per month for >3 months, fulfilling any of the following:

1. criteria C and D for 1.1 Migraine without aura
2. criteria B and C for 1.2 Migraine with aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3. 2018

1.3 慢性偏頭痛 Chronic migraine

A. 頭痛(可以類偏頭痛(migraine-like)及/或類緊縮型(tension-type-like))發作每月≥ 15天，已 > 3個月，且符合基準B及C

B. 發生於已經有至少五次發作符合基準1.1*無預兆偏頭痛*B-D項及/或1.2*預兆偏頭痛*B及C項的病人

C. 發作每月≥8天，已>3個月，且符合下列之一：

1. 基準1.1*無預兆偏頭痛* C及D項
2. 基準1.2*預兆偏頭痛* B及C項
3. 開始發作時病人相信是偏頭痛發作，而且使用翠普登(triptan)或麥角鹼藥物(ergot derivative)可達到緩解

D. 沒有其他更合適的ICHD-3診斷

ICHD-3. 2018

Quiz:

A patient having headache on 25 days/month meeting

migraine criteria on 8 days and

tension-type headache criteria on 17 days

Diagnosis?

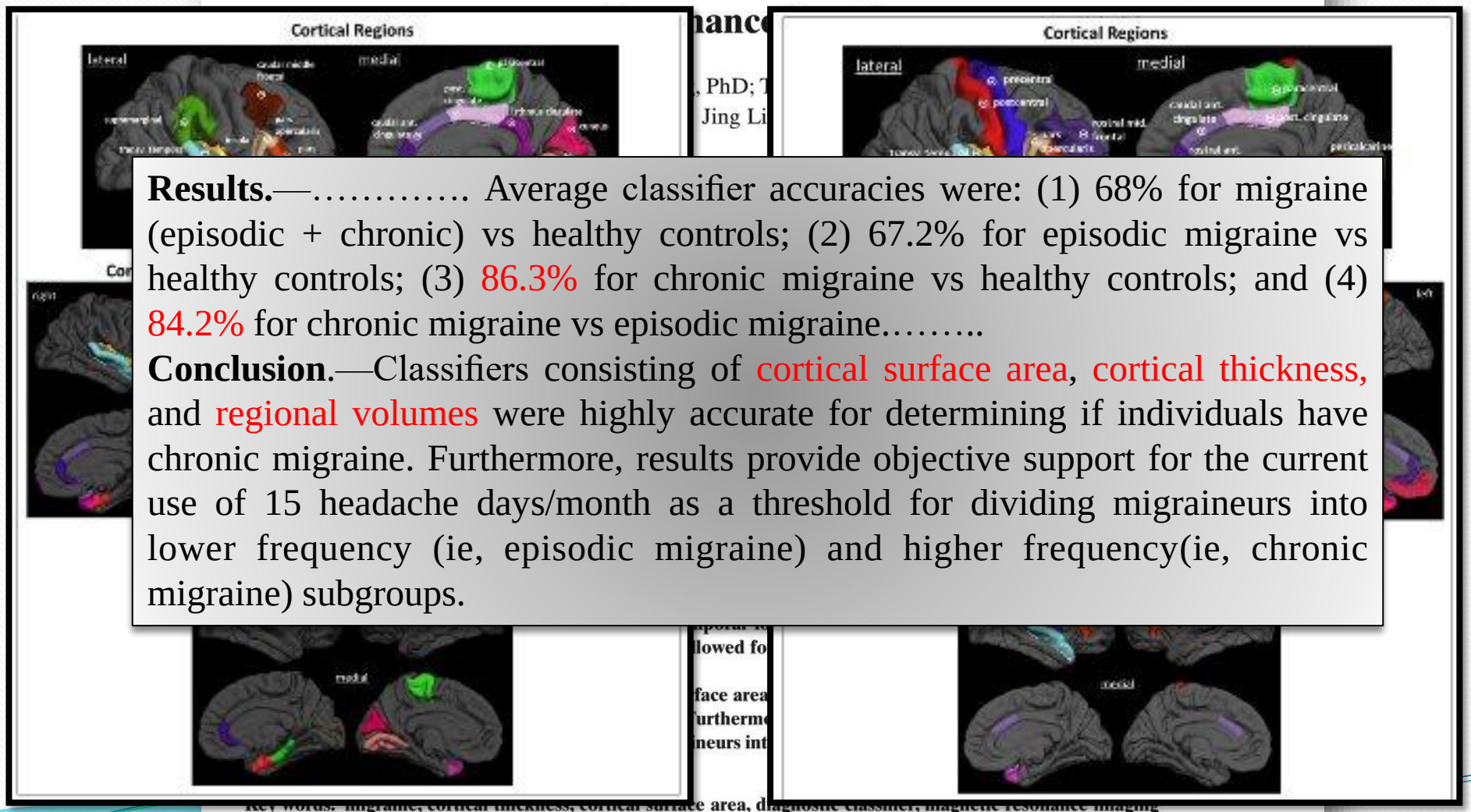
1. Chronic migraine
2. Chronic tension-type headache
3. Both

Answer: 1

- Because[illegible] criteria for 1.3 *Chro*[illegible] of 2. *Tension-*[illegible]

2015 Harold G. Wolff Award Paper

Accurate Classification of Chronic Migraine via Brain Magnetic

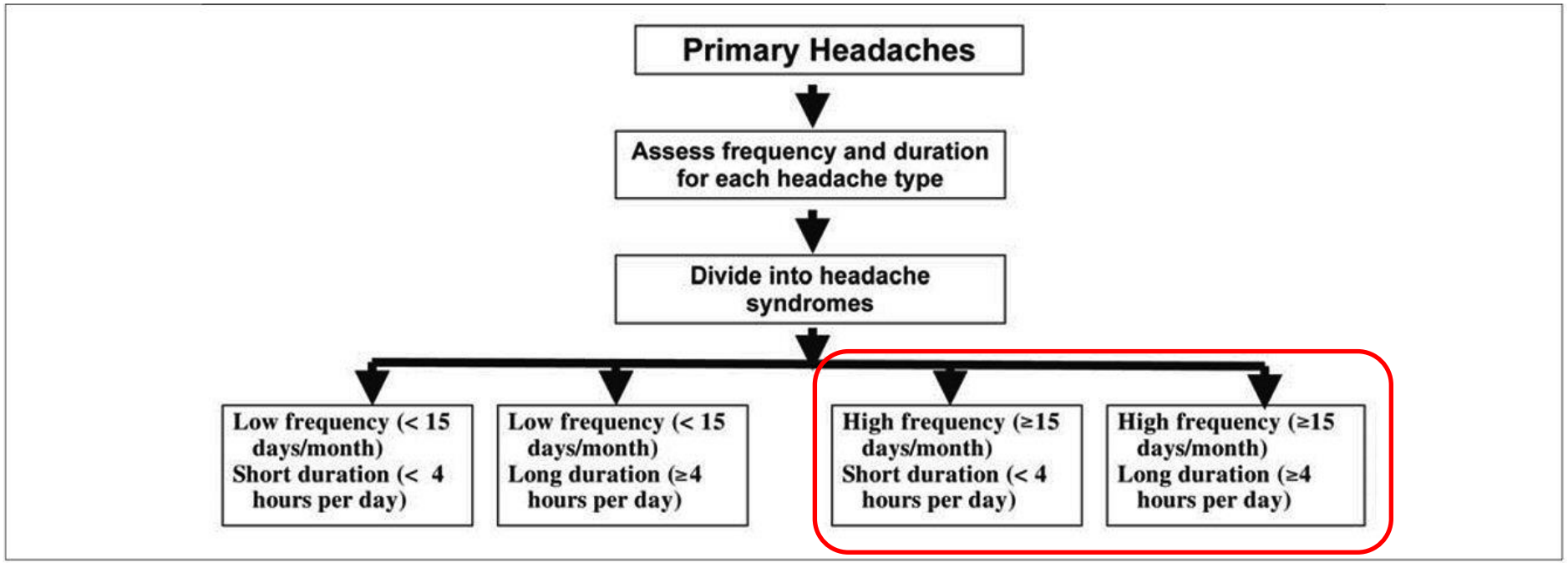


Results.—……. Average classifier accuracies were: (1) 68% for migraine (episodic + chronic) vs healthy controls; (2) 67.2% for episodic migraine vs healthy controls; (3) 86.3% for chronic migraine vs healthy controls; and (4) 84.2% for chronic migraine vs episodic migraine……..

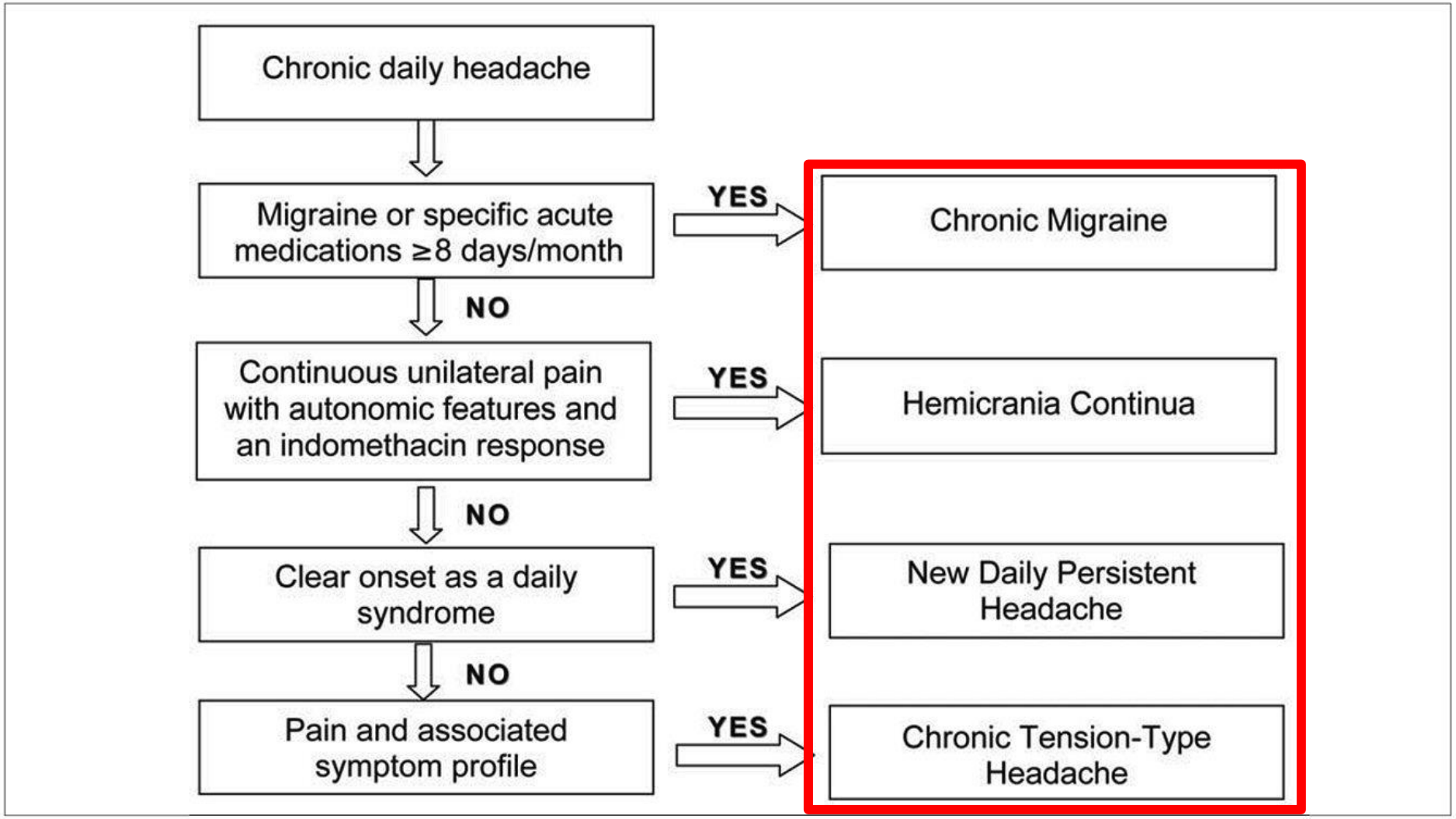
Conclusion.—Classifiers consisting of cortical surface area, cortical thickness, and regional volumes were highly accurate for determining if individuals have chronic migraine. Furthermore, results provide objective support for the current use of 15 headache days/month as a threshold for dividing migraineurs into lower frequency (ie, episodic migraine) and higher frequency(ie, chronic migraine) subgroups.

Headache. 2015;55:762-77

Differential diagnosis

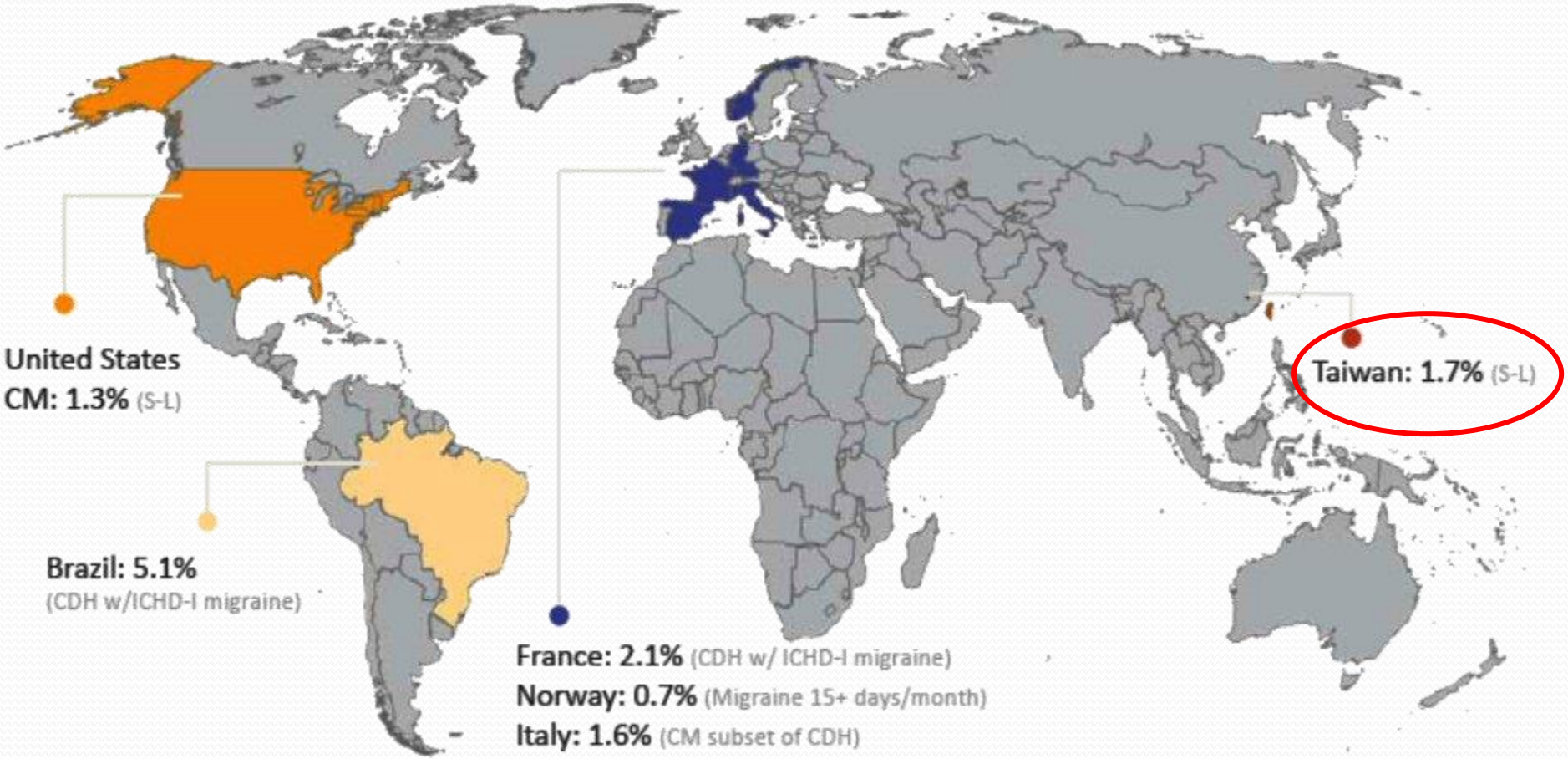


J Headache Pain. 2007;8:263-72.



J Headache Pain. 2007;8:263-72.

Chronic Migraine: Global Prevalence*
Based on Reports in Literature



*Due to the heterogeneity of studies, some variation in definitions of chronic migraine exists.
CDH = chronic daily headache; S-L = Silberstein-Lipton definition of chronic migraine.

Natoli J et al. *Cephalalgia*. 2009. E-pub ahead of print.
Silberstein SD et al. Neurology. 1996;47:871-875

Chronic Migraine Prevalence, Disability, and Sociodemographic Factors: Results From the American Migraine Prevalence and Prevention Study

Dawn C. Buse, PhD; Aubrey N. Manack, PhD; Kristina M. Fanning, PhD; Daniel Serrano, PhD; Michael L. Reed, PhD; Catherine C. Turkel, PhD, PharmD; Richard B. Lipton, MD

- CM prevalence rate of nearly 1%
- Prevalence to be highest for both sexes in midlife
- Representing 7.68% of all migraine cases

- 75% of those with CM are undiagnosed*

Headache. 2012;52:1456-70
*Neurology. 2019;92:P4.10–004

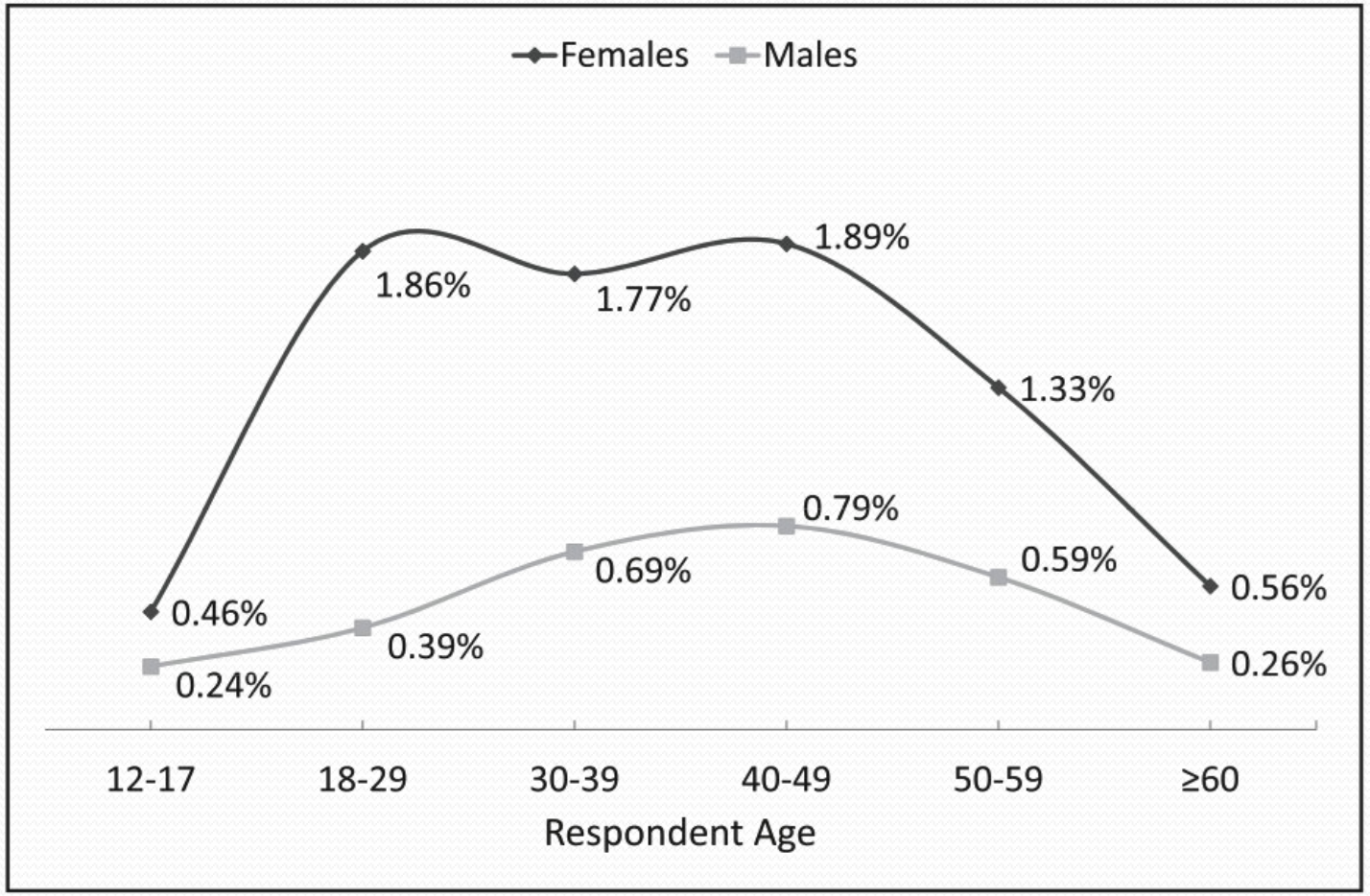
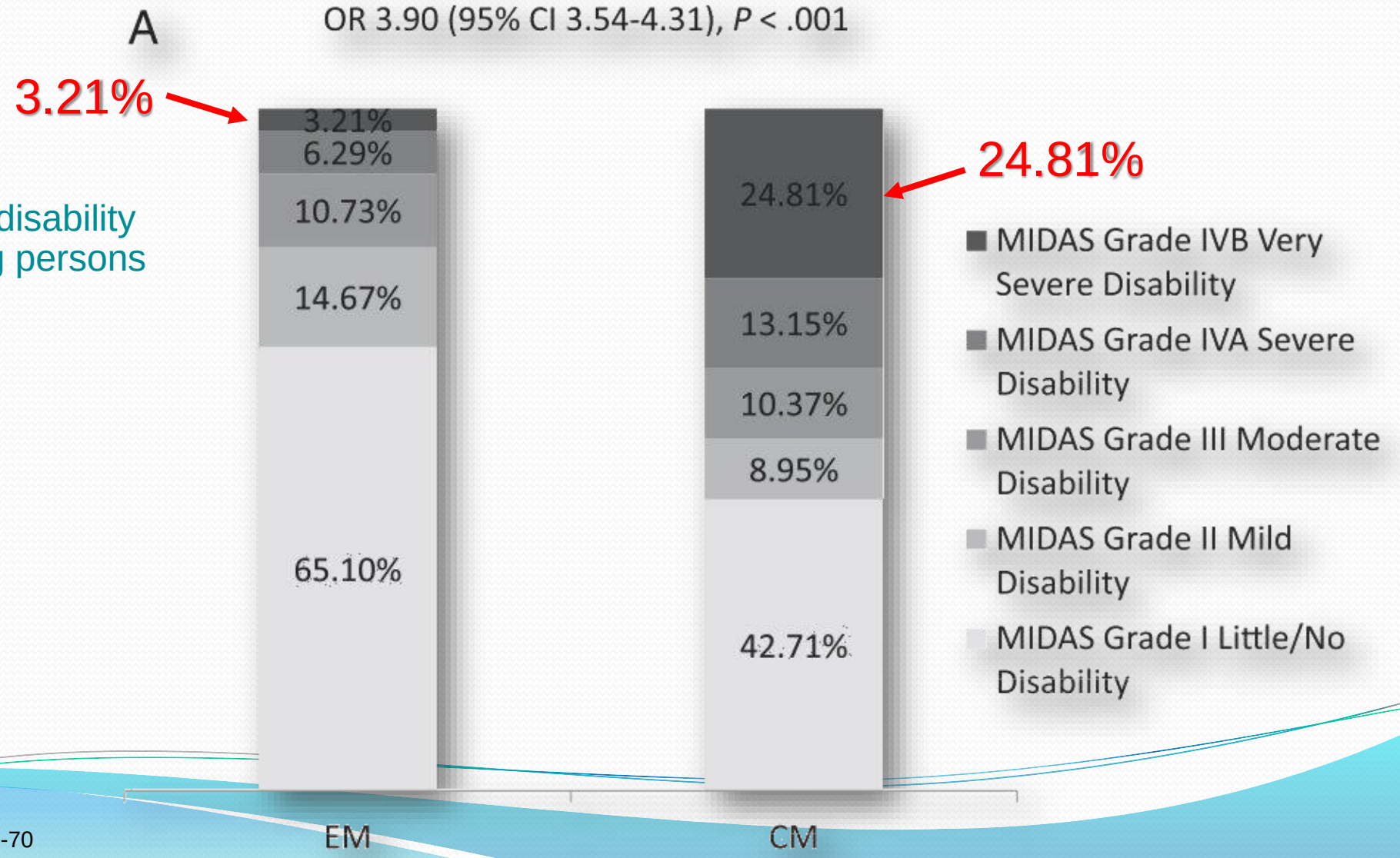


Fig 1.—Adjusted prevalence of chronic migraine by sex and age. Results from general linear model adjusting for sociodemographics (race, ethnicity, geographic region, population density, income, and household size).

Headache. 2012;52:1456-70

Disability, EM vs. CM

- Severe headache-related disability was more common among persons with CM



Buse DC, et al. Headache. 2012;52:1456-70

Research Submissions

Economic Burden of Transformed Migraine: Results From the American Migraine Prevalence and Prevention (AMPP) Study

Julie Munakata, MS; Elisabeth Hazard, PhD; Daniel Serrano, MS; David Klingman, PhD; Marcia F.T. Rupnow, PhD; Jonothan Tierce, CPhil; Michael Reed, PhD; Richard B. Lipton, MD

Objective.—To evaluate the impact of incident transformed migraine on health care resource utilization, medication use, and productivity loss. In addition, the study estimates the total direct and indirect costs associated with transformed migraine.

Background.—Emerging evidence indicates that migraine may be a chronic progressive disorder characterized by escalating frequency of headache attacks, often termed transformed migraine. Little is known about the economic impact of transformed migraine.

Methods.—AMPP is a 5-year, national, longitudinal survey study of headache in the US. The study utilized data from the 2006 follow-up survey based on an initial sample of 14,544 adults identified as having migraine in either the 2004 screening or 2005 baseline survey. A diagnosis of migraine was assigned based on criteria proposed by the International Classification of Headache Disorders, 2nd Edition [illegible] questionnaires on headache features, frequency, impairment, resource [illegible] direct headache-related costs were estimated using unit cost assumpti[illegible] lesale acquisition costs (Red Book), and wage data from the US Burea[illegible] migraine were compared with those who did not develop transformed [illegible] eline and follow-up.

CM vs. EM
$7750 vs. $1757

Results.—A total of 7796 (54[illegible] p survey. Of those cases, 359 (4.6%) developed transformed migraine. Participants who developed transformed migraine reported significantly more primary care visits, neurologist or headache specialist visits, pain clinic visits, and emergency room visits compared with participants whose migraine remained episodic. Hospital nights and urgent care visits did not reach statistical significance. Transformed migraine participants reported significantly more time missed at work or school because of headaches and more time where work or school productivity was reduced by >50% in the previous 3 months because of headaches. Average per-person annual total costs, including direct and indirect costs, were 4.4-fold greater for those who developed transformed migraine ($7750) compared with those who remained episodic ($1757).

Conclusion.—Transformed migraine exacts a significantly higher economic toll on patients and health care systems compared with other forms of migraine. Our findings support the need to prevent migraine progression and to provide appropriate management and treatment of transformed migraine.

Key words: migraine, transformed migraine, economic, productivity loss, resource utilization

Headache. 2009;49:498-508

Cost of Chronic and Episodic Migraine: a pilot study from a tertiary headache centre in northern Italy

E Berra[1*], G Sances[1], R De Icco[2], M Avenali[2], M Berlangieri[2], I De Paoli[2], M Bolla[3], M Allena[1], N Ghiotto[1], E Guaschino[1], S Cristina[1], C Tassorelli[1,2], G Sandrini[1,2] and G Nappi[1]

Abstract

Background: Chronic migraine (CM) has a high impact on functional performance and quality of life (QoL). CM also has a relevant burden on the National Health Service (NHS), however precise figures are lacking. In this pilot study we compared the impact in terms of costs of CM and episodic migraine (EM) on the individual and on the National Health System (NHS). Furthermore, we comparatively evaluated the impact of CM and EM on functional capability and on QoL of sufferers.

Methods: We enrolled 92 consecutive patients attending the Pavia headache centre: 51 subjects with CM and 41 with EM. Patients were tested with disability scales (MIDAS, HIT-6, SF-36) and with an *ad hoc* semi-structured questionnaire.

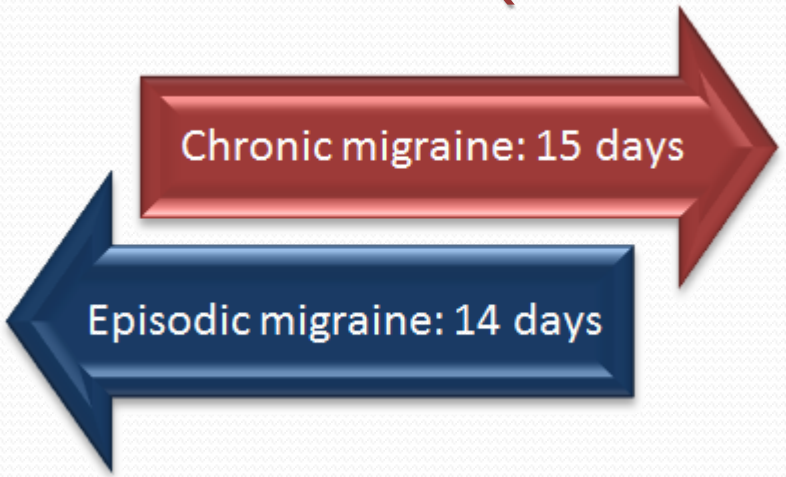
Results: The direct mean annual cost (in euro) per patient suffering from CM was €2250.0 ± 1796.1, against €523.6 ± 825.8 per patie 58.3 ± 801.8 for EM. The total economic load a M vs. EM p = 0.001 for each value).
CM subjects had higher s IT-6 (66.1 ± 8.4 vs 58.7 ± 10.1, p = 0.001). The

CM vs. EM
€2250.0 vs. €523.6

Conclusions: CM is a disabling condition with a huge impact on the QoL of sufferers and a significant economic impact on the NHS. The adequate management of CM, reverting it back to EM, will provide a dual benefit: on the individual and on the society.

Keywords: Migraine; Chronic migraine; Episodic migraine; Cost; Resource utilization; Italy

3% per year
(14% in special clinic)

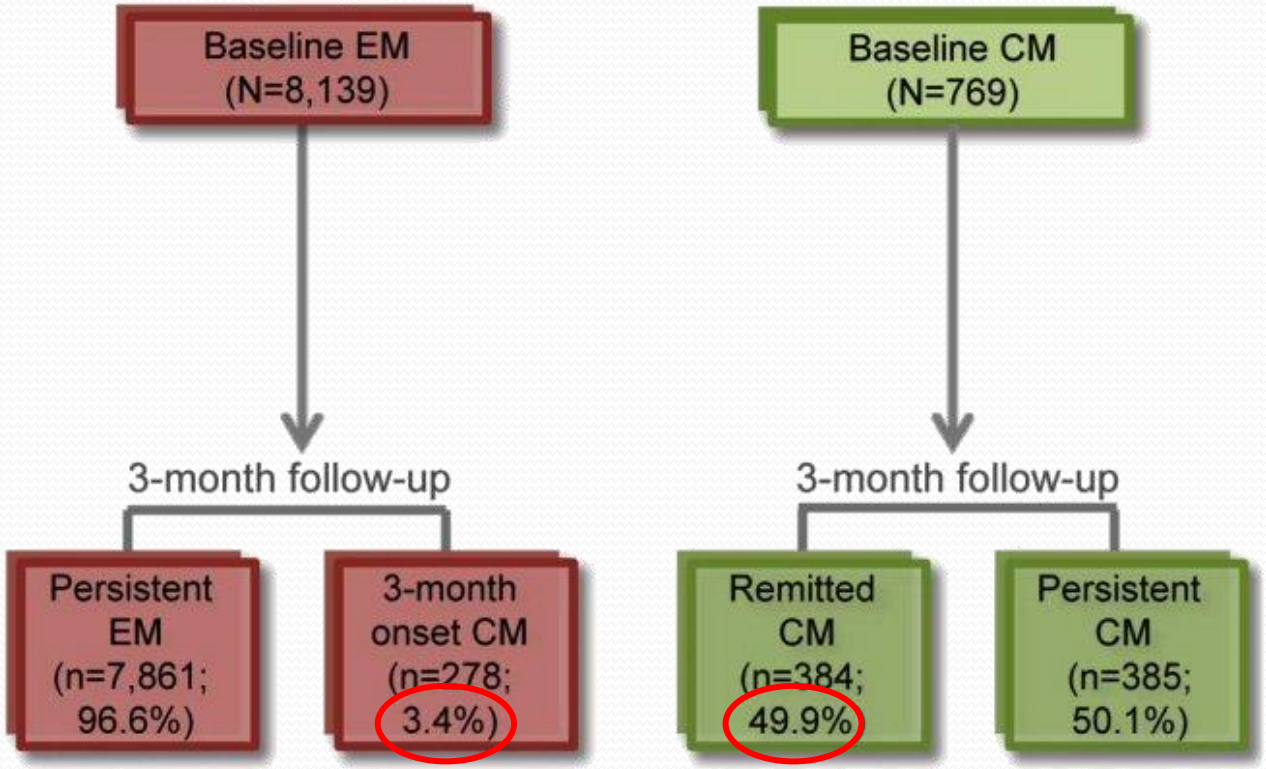


65% in 2 years
66% no longer has persistent CM in 2 years

Pain.2003;106:81-89
Neurology. 2004;62:788-790
Cephalalgia. 2001;21:980-6
Neurology. 2011;76:711-8

Chronic Migraine Epidemiology and Outcomes (CaMEO) Study

Figure 2 Transition in headache-day status



Transition in headache-day status from baseline to 3-month follow-up. CM = chronic migraine (≥15 headache-days per month); EM = episodic migraine (<15 headache-days per month).

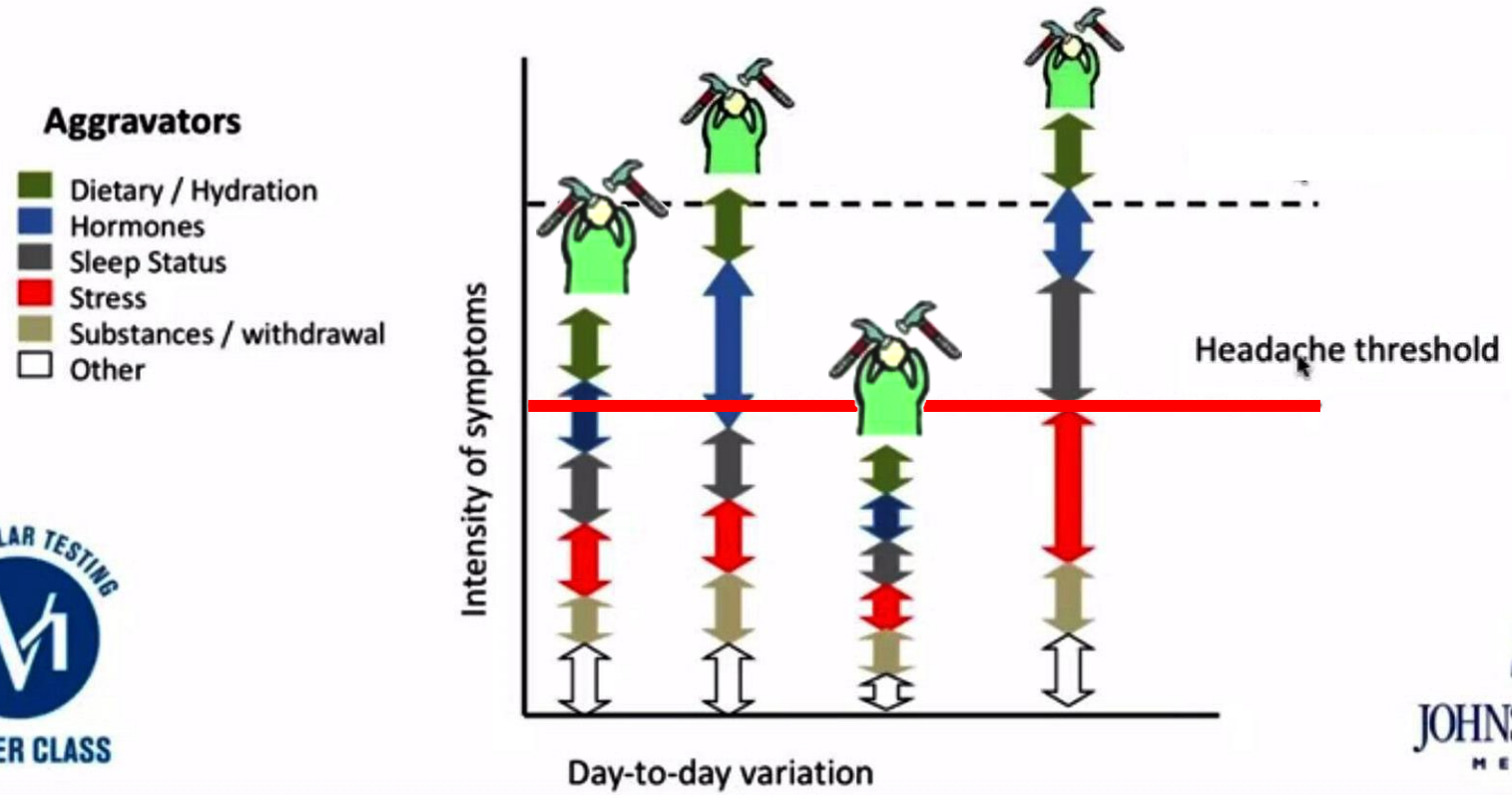
Neurology 2017;89:461–468

Chronic migraine as a threshold disorder

- Migraine is a cyclic disorder susceptibility to certain attack-triggering stimuli.
- Interictal state, threshold is normal and susceptibility to stimuli is relatively low.
- Oscillating changes, probably originating from the limbic system, drive periodical decreases in thresholds.
- If the threshold sinks beneath a certain value, certain physiological changes lead to migraine attack.

Nat Rev Neurol. 2016;12:455-64

Vestibular migraine-threshold paradigm



VESTIBULAR TESTING MASTER CLASS

JOHNS HOPKINS MEDICINE

Courtesy of Dr. Amir Kheradmand

CM as a threshold disorder

- **General risk factors**: obesity, depression and stressful life events might lower the threshold.
- **Increasing attack frequency**: shortens the interictal period so that the threshold might not restore to baseline level.
- **Sensitization processes**: might lower the threshold. **allodynia**
- **Insufficient acute headache medication**: could lead to longer-lasting central sensitization and predisposes to migraine progression.

Nat Rev Neurol. 2016;12:455-64

Protective factors

- **Physical exercise**, **stress management**, and **preventive medication**, might increase the threshold and thereby counteract the chronification process.

Nonmodifiable risk factors

- Age (18-29 years and 40-49 years)
- Female sex (3:1)
- Low educational status
- Low socioeconomic status

Nat Rev Neurol. 2016;12:455-64

Modifiable risk factors

- Overuse of acute migraine medication
- Ineffective acute treatment
- Obesity
- Depression, other psychological and personality factors
- Stressful life events, such as divorce or being recently widowed

Nat Rev Neurol. 2016;12:455-64

Reversion to episodic migraine

- Lower baseline headache frequency
- Absence of cutaneous allodynia

- Adherence to migraine prophylactic drugs
- Withdrawal of overused migraine abortive drugs
- Physical exercise

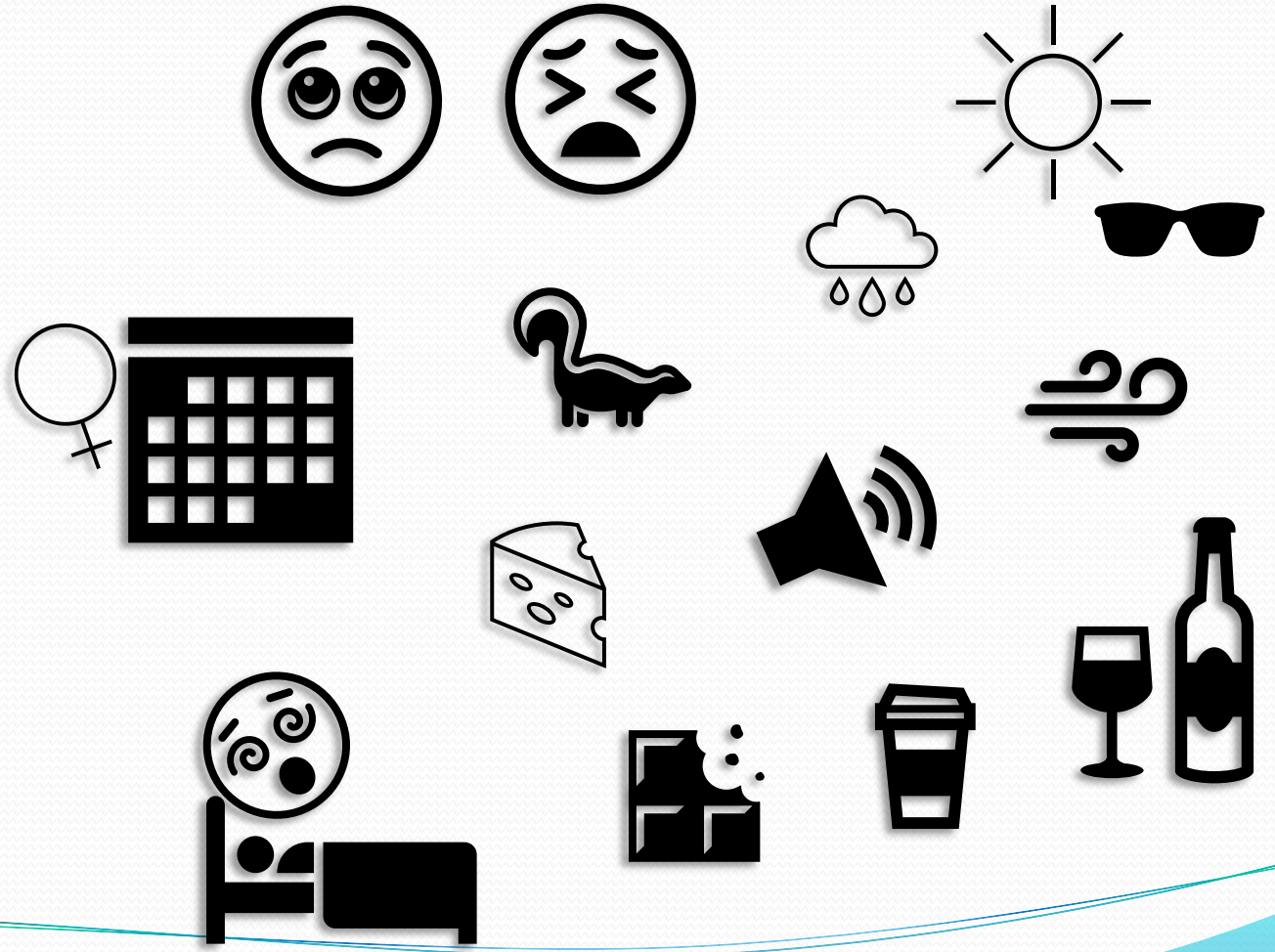
BMJ 2014;348:g1416

Treatment for chronic migraine

- Trigger avoidance
- Abortive treatment
- Preventive treatment

Triggers of Migraine

- Multiple studies clearly demonstrate triggers in episodic migraine, often related to change in homeostasis or environment. Many common migraine triggers are not easily modifiable and avoiding triggers may not be realistic. Healthy lifestyle choices such as exercise, adequate sleep, stress management, and eating regularly may prevent triggers and transformation to chronic migraine over time.



1. Marmura, M.J. Curr Pain Headache Rep 22, 81 (2018)

藥物種類（建議劑量 mg/d）	在急性偏頭痛治療中的注意事項	證據強度	推薦等級
翠普登 Triptans			
Sumatriptan (50 -100)	中重度偏頭痛，或第一線治療無效之輕中度偏頭痛	A	I
Sumatriptan (20) in	合併嚴重噁心嘔吐，或需非腸道給藥途徑時。 兒童患者若需使用翠普登只建議鼻噴劑	A	I
Rizatriptan (5-10)	同 sumatriptan，但療效略佳	A	I
麥角胺 Ergotamine			
Ergotamine/caffeine (1/100)	懷孕及授乳婦女、心血管、腦血管疾病、雷諾氏症 與腎衰竭患者，禁止使用此藥	B	II

單純止痛藥 Simple Analgesics			
Acetaminophen (1000)	孕婦及兒童的首選用藥。建議於輕中度偏頭痛使用。	A	I
非類固醇抗發炎藥物 NSAID			
Ibuprofen (200-400)	輕中度偏頭痛的第一線治療，兒童患者的第一線治療	A	I
Naproxen (750)	輕中度偏頭痛的第一線治療	A	I
Dicofenac (50-100)		A	I
Aspirin (900-1000)		A	I
其他 NSAID	同上，適用於輕中度偏頭痛	B	II
Ketorolac (30-60, im), (30, iv)	急診使用	B	II
Cox-2 inhibitors	需注意心血管的副作用	C	IV

複方止痛製劑 FDC			
AAC tablet (acetaminophen 500 – aspirin 500 -caffeine 130)	發作情形相對輕微時，選擇性使用，避免過度使用	A	II
止吐劑 Antiemetics			
Prochlorperazine (10 im)	其他急性治療之輔助用藥，有止吐效果	B	II
Metoclopramide (10 im, iv)		B	II
Chlorpromazine (25 iv)	副作用大，不做為第一線用藥。 重積狀態可考慮使用。	B	IV
Droperidol (2.75 iv)		B	IV
其他類 Others			
Steroids (iv) (dexamethasone 12-20; hydrocortisone 100-250)	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	C	III
Magnesium (1000-2000 iv)	無定論，可能只對特定 (血清鎂過低且屬預兆型)	B	IV

Lasmiditan, New 5-HT_{1F} Agonist Acute Migraine Medication

- 2-hour pain freedom is about 30% (placebo <20%)
- Adverse events are mild to moderate dizziness and somnolence at 10-15%, less than described for rizatriptan in the prescribing information
- The lasmiditan adverse events are likely due to activation of the 5-HT_{1F} receptors, which are mostly central
- 5-HT_{1F} receptors do not cause vasoconstriction, so unlike triptans, this new class should be safe in the presence of vascular disease

(Oct 11, 2019) FDA Approves Reyvow (lasmiditan), the First Serotonin (5-HT) 1F Receptor Agonist for the Acute Treatment for Migraine

1. Kuca B, et al. Presented at Diamond Headache Clinic Research & Educational Foundation Headache Update 2017; Lake Buena Vista, FL. 2. Wietecha LA, et al. Abstract PO-02-180 presented at IHC 2017; Vancouver.

Curtesy of Dr. Tepper

The Small Molecule CGRP Receptor Antagonists: Gepant Summary

Acute Treatment of Episodic Migraine

- There have been 6 gepants tested which demonstrated efficacy in acute migraine treatment: olcegepant, BI 44370 TA, telcagepant, MK-3207, rimegepant, and ubrogepant
- BI 44370 TA, telcagepant, and MK-3207 are all reportedly liver toxic
- **Ubrogepant and rimegepant** have reported out positive
  acute treatment of migraine over the next ye
- 2-hour pain freedom ≈ 20%
- They do not cause blood vessels to constrict, so, unlike tri
- They work more like naratriptan or DHE than sumatriptan:

(Dec 23, 2019) FDA Approves Ubrelvy (ubrogepant) for the Acute Treatment of Migraine
(Feb 27, 2020) FDA Approves Nurtec ODT (rimegepant) for the Acute Treatment of Migraine in Adults

Preventive Treatment of Episodic Migraine

- **Atogepant** vs placebo reported out positive phase 2 trial in 2018, will proceed to phase 3 trials, and showed drops in mean monthly migraine days for episodic migraine similar to the MABs
- No significant liver signal
- **Rimegepant** will be tested for prevention in phase 2

1. Tfelt-Hansen P. *Headache*. 2011;51:118-123. 2. Tfelt-Hansen P, Do TP. Abstract PO-01-48 presented at IHC 2017; Vancouver. 3. Allergan press release. February 6, 2018. https://www.allergan.com/news/news/thomson-reuters/allergan-announces-positive-top-line-phase-3-resul. Accessed April 26, 2018. 4. Biohaven press release. March 26, 2018. http://biohavenpharma.com/biohaven-announces-successful-achievement-of-both-co-primary-regulatory-endpoints-in-two-pivotal-phase-3-trials-of-rimegepant-an-oral-cgrp-receptor-antagonist-for-the-acute-treatment-of-migraine/. Accessed April 26, 2018.

Curtesy of Dr. Tepper

何時需要開始預防性治療?

a) 反覆偏頭痛發作，明顯影響病患的生活品質或日常活動，且已經排除誘發因素，妥善使用急性治療藥物和改善生活型態；

b) 頻繁的偏頭痛發作，其次數超過每月4次，或天數超過每月8天，有進展成慢性偏頭痛的可能；

c) 急性治療藥物治療失敗、使用禁忌或使用過量者；

d) 病患個人意願，想要盡可能減少發作次數；

e) 特殊形式偏頭痛發作，如偏癱偏頭痛(hemiplegic migraine)、腦幹預兆偏頭痛(migraine with brain stem aura)、過長或令人不適的預兆期(prolonged aura)、或偏頭痛腦梗塞(migrainous infarction)等；

OnabotulinumtoxinA for Treatment of Chronic Migraine: Poole

Randomized, P

PRE

David

Silber

Group

Affilia

PMID:

Onabotul

Migraine

Randomi

PREEMPT

H C Diener [1], D

Brin, PREEMPT 2

Collaborators, Af

PMID: 20647171

RESEARCH ARTICLE Open Access

Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study

Andrew M. Blumenfeld[1*], Richard J. Stark[2], Marshall C. Freeman[3], Amelia Orejudos[4] and Aubrey Manack Adams[4]

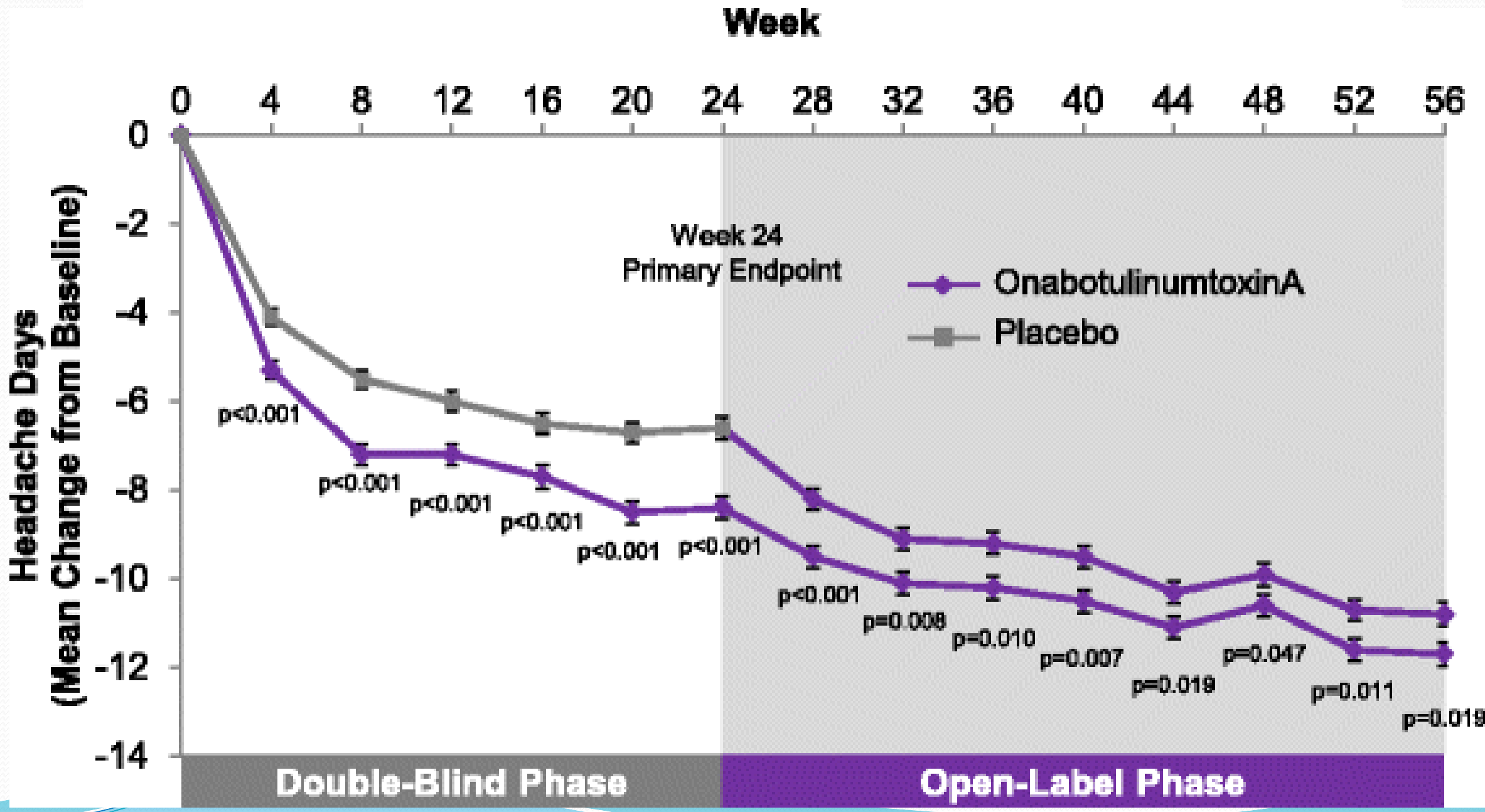
Abstract

Background: OnabotulinumtoxinA is approved for the prevention of headache in those with chronic migraine (CM); however, more clinical data on the risk-benefit profile for treatment beyond one year is desirable.

Methods: The Chronic Migraine OnabotulinuMtoxinA Prolonged Efficacy open Label (COMPEL) Study (ClinicalTrials.gov, NCT01516892) is an international, multicenter, open-label long-term prospective study. Adults with CM received 155 U of onabotulinumtoxinA (31 sites in a fixed-site, fixed-dose paradigm across 7 head/neck muscles) every 12 weeks (±7 days) for 9 treatment cycles (108 weeks). The primary outcome was headache day reductions at 108 weeks; secondary outcomes were headache day reductions at 60 weeks and change in the 6-item Headache Impact Test (HIT-6) score. Safety and tolerability were assessed by reviewing the frequency and nature of adverse events (AEs).

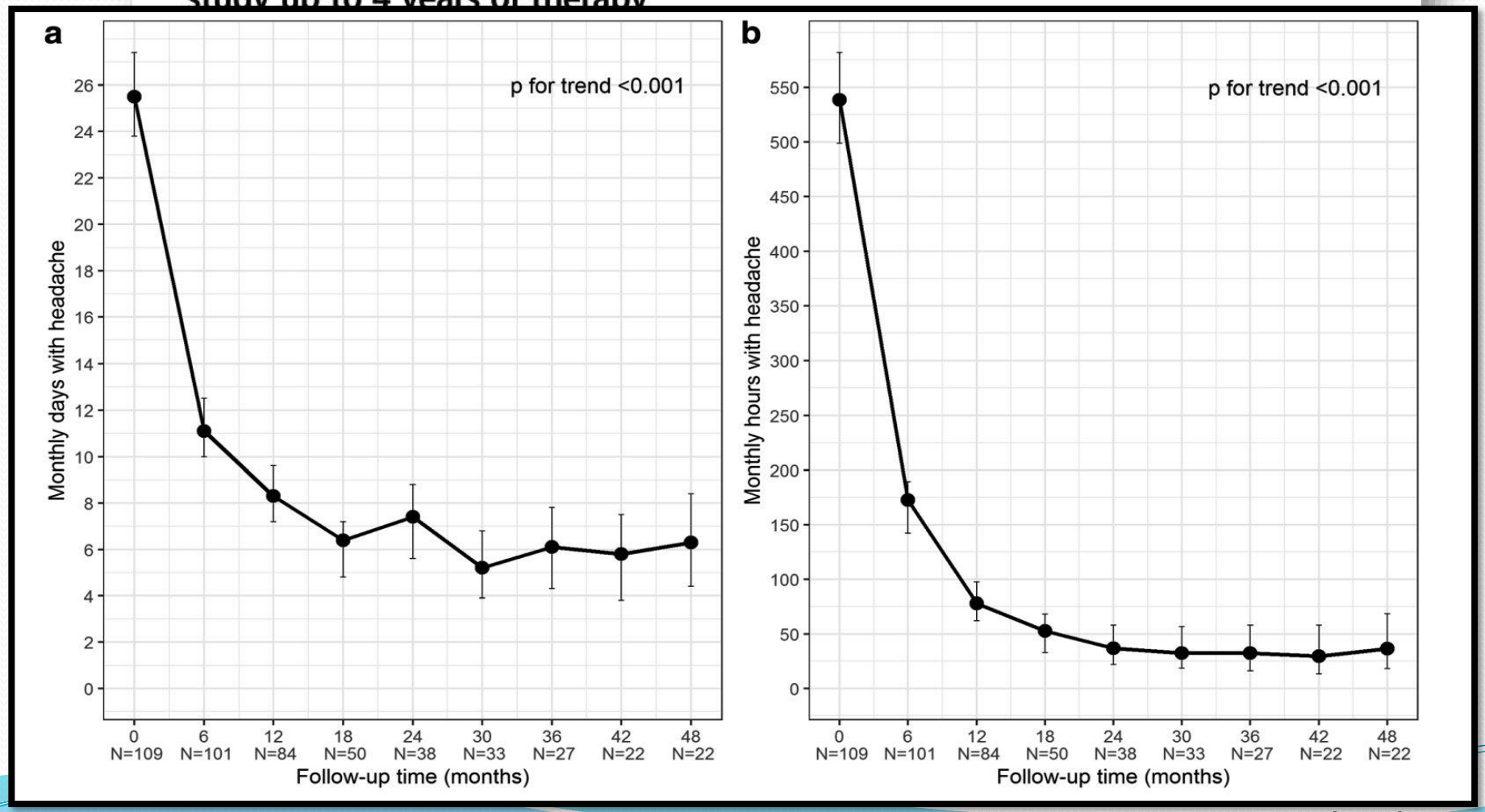
Headache 2010;50:921-36.
Cephalalgia 2010;30:804-14.
J Headache Pain. 2018;19:13

活水 Living Water


Week
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
Headache Days
(Mean Change from Baseline)
0
-2
-4
-6
-8
-10
-12
-14
Week 24
Primary Endpoint
OnabotulinumtoxinA
Placebo
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p=0.008
p=0.010
p=0.007
p=0.019
p=0.047
p=0.011
p=0.019
Double-Blind Phase
Open-Label Phase

ORIGINAL ARTICLE

Chronic migraine long-term regular treatment with onabotulinumtoxinA: a retrospective real-life observational study up to 4 years of therapy



Neurol Sci . 2020;41:1809-1820.

Topiramate in the Treatment of Chronic Migraine

M Silvestrini [1], M Bartolini, M Coccia, R Baruffaldi, R Taffi, L Provinciali

Affiliations + expand

PMID: 14510929 DOI: 10.1046/j.1468-2982.2003.00592.x

Abstract

The purpose of this study wa
migraine. This was a double-
suffering from chronic migra
receive topiramate or placeb
in 25-mg increments over or
maintenance phase. Numbe
At baseline, there was no dif
with topiramate and those tr
respectively). During the last
significantly lower 28-day he
number of days with headac
doses proved to be an effect
chronic migraine and analge

Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study

H-C Diener[1], G Bussone[2], JC Van Oene[3], M Lahaye[3], S Schwalen[3] & PJ Goadsby[4,5] on behalf of the TOPMAT-MIG-201(TOP-CHROME) Study Group*

[1]Department of Neurology, University of Duisburg-Essen, Germany, [2]Department of Neurology, 'C. Besta' Neurological Institute, Milan, Italy, [3]Janssen-Cilag EMEA, Tilburg, the Netherlands and Neuss, Germany, [4]Institute of Neurology, London, UK and [5]Department of Neurology, University of California, San Francisco, CA, USA

Cephalalgia

Diener H-C, Bussone G, Van Oene JC, Lahaye M, Schwalen S & Goadsby PJ on behalf of the TOPMAT-MIG-201(TOP-CHROME) Study Group. Topiramate ys in chronic migraine: a randomized, double-blind, dy. Cephalalgia 2007; 27:814–823. London. ISSN 0333-1024

was to evaluate the efficacy and tolerability of topiramate hronic migraine in a randomized, double-blind, placebo- ic migraine is a common form of disabling headache e subspecialty practice. Preventive treatments are essential management, although there are few or no controlled n their use in this patient population. Topiramate is phylaxis of migraine headache in adults. Patients (18–

Headache
© 2007 the Authors
Journal compilation © 2007 American Headache Society

ISSN 0017-8748
doi: 10.1111/j.1526-4610.2006.00684.x
Published by Blackwell Publishing

Research Submissions

Efficacy and Safety of Topiramate for the Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Trial

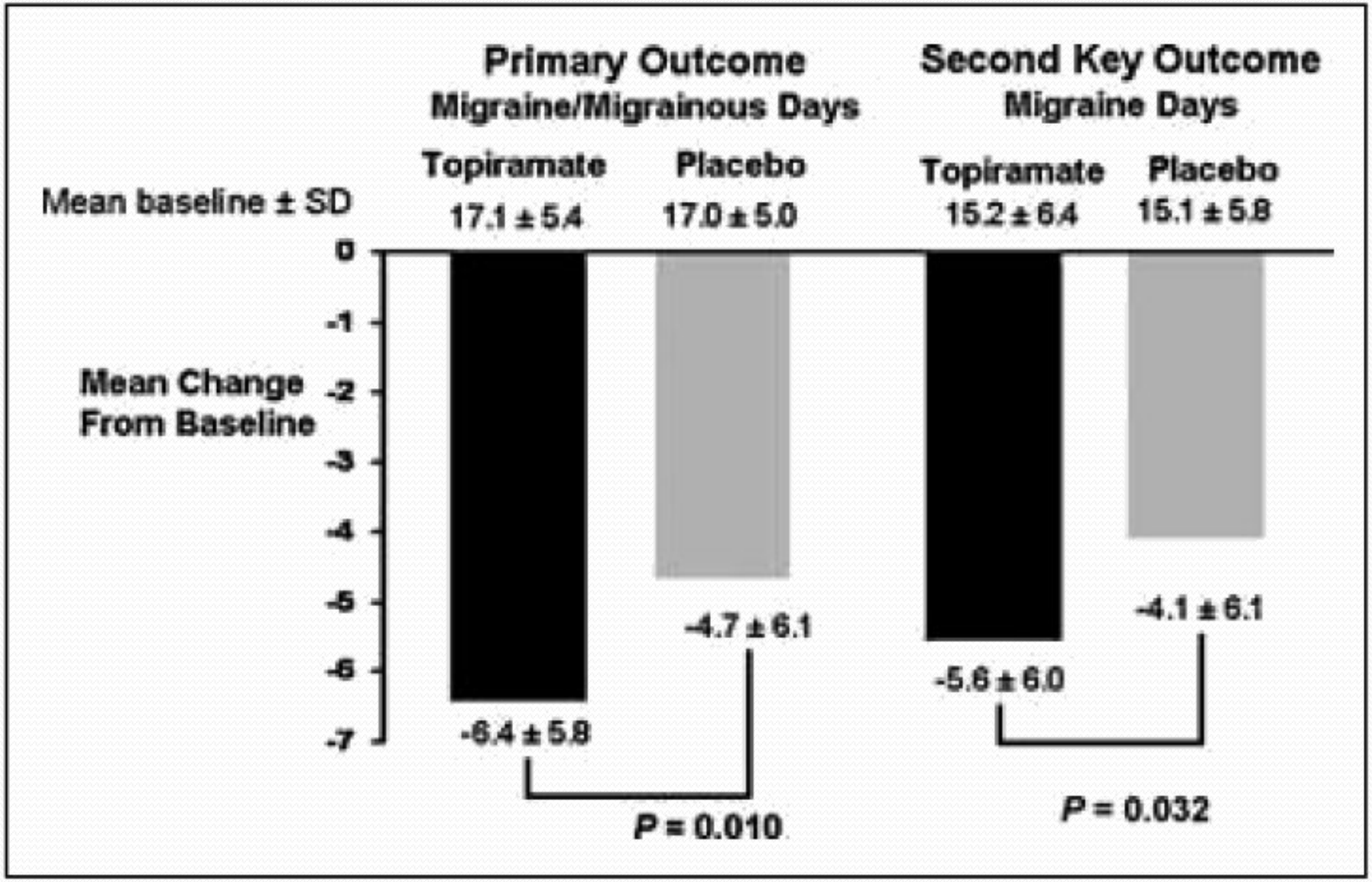
Stephen D. Silberstein, MD; Richard B. Lipton, MD; David W. Dodick, MD; Frederick G. Freitag, DO; Nabih Ramadan, MD; Ninan Mathew, MD; Jan L. Brandes, MD; Marcelo Bigal, MD; Joel Saper, MD; Steven Ascher, PhD; Donna M. Jordan, RN; Steven J. Greenberg, MD; Joseph Hulihan, MD; on behalf of the Topiramate Chronic Migraine Study Group

Objective.—To evaluate the efficacy and safety of topiramate (100 mg/day) compared with placebo for the treatment of chronic migraine.

Methods.—This was a randomized, placebo-controlled, parallel-group, multicenter study consisting of 16 weeks of double-blind treatment. Subjects aged 18 to 65 years with 15 or more headache days per month, at least half

Cephalalgia 2003;23:820-4.
Cephalalgia 2007;27,814–23
Headache 2007;47:170-180

活水 Living Water



Headache 2007;47:170-180

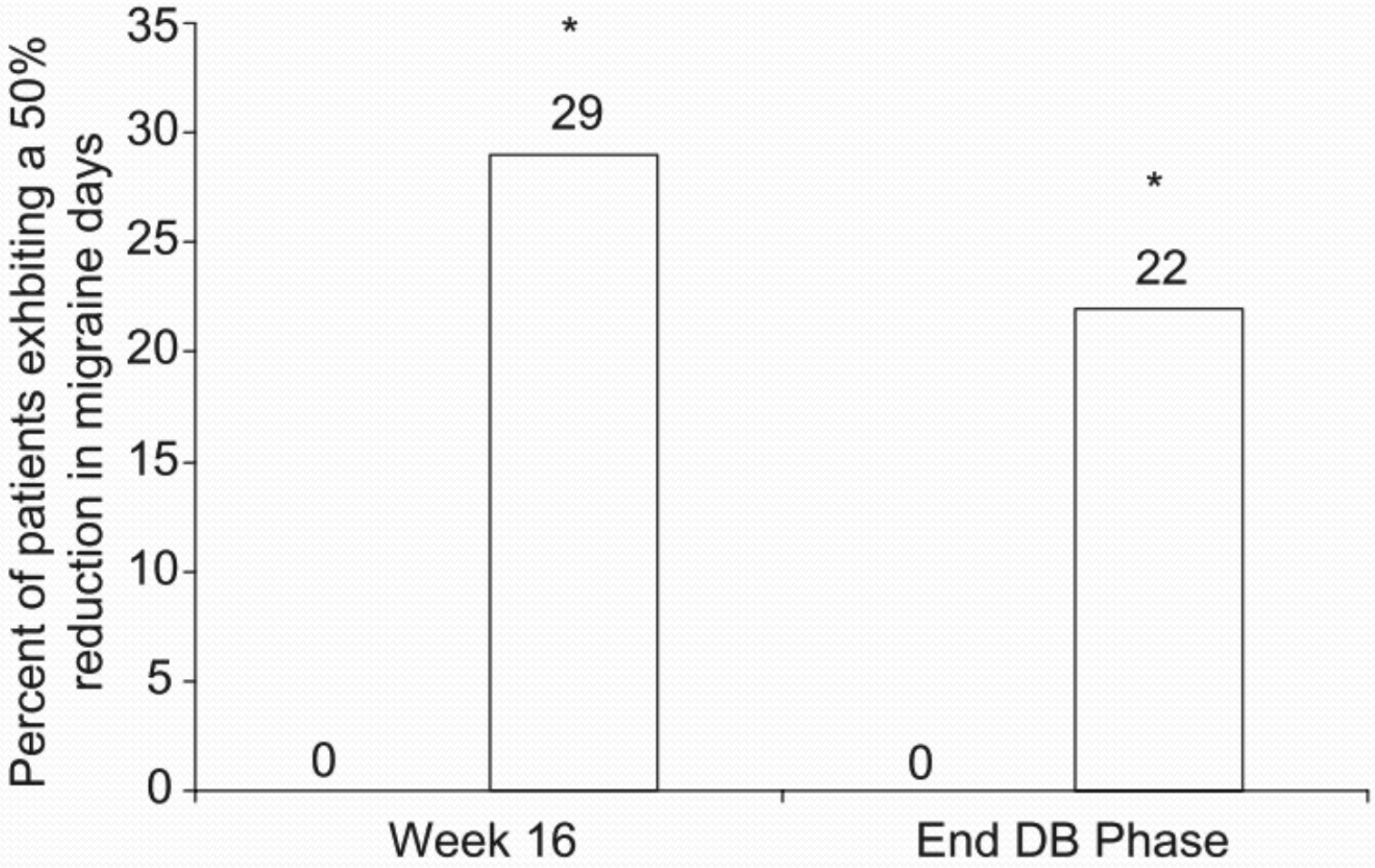


Figure 4 Rate of responders (50% reduction in migraine days). ■, Placebo; □, topiramate. *$P < 0.04$ vs. placebo.

Cephalalgia 2007;27,814–23

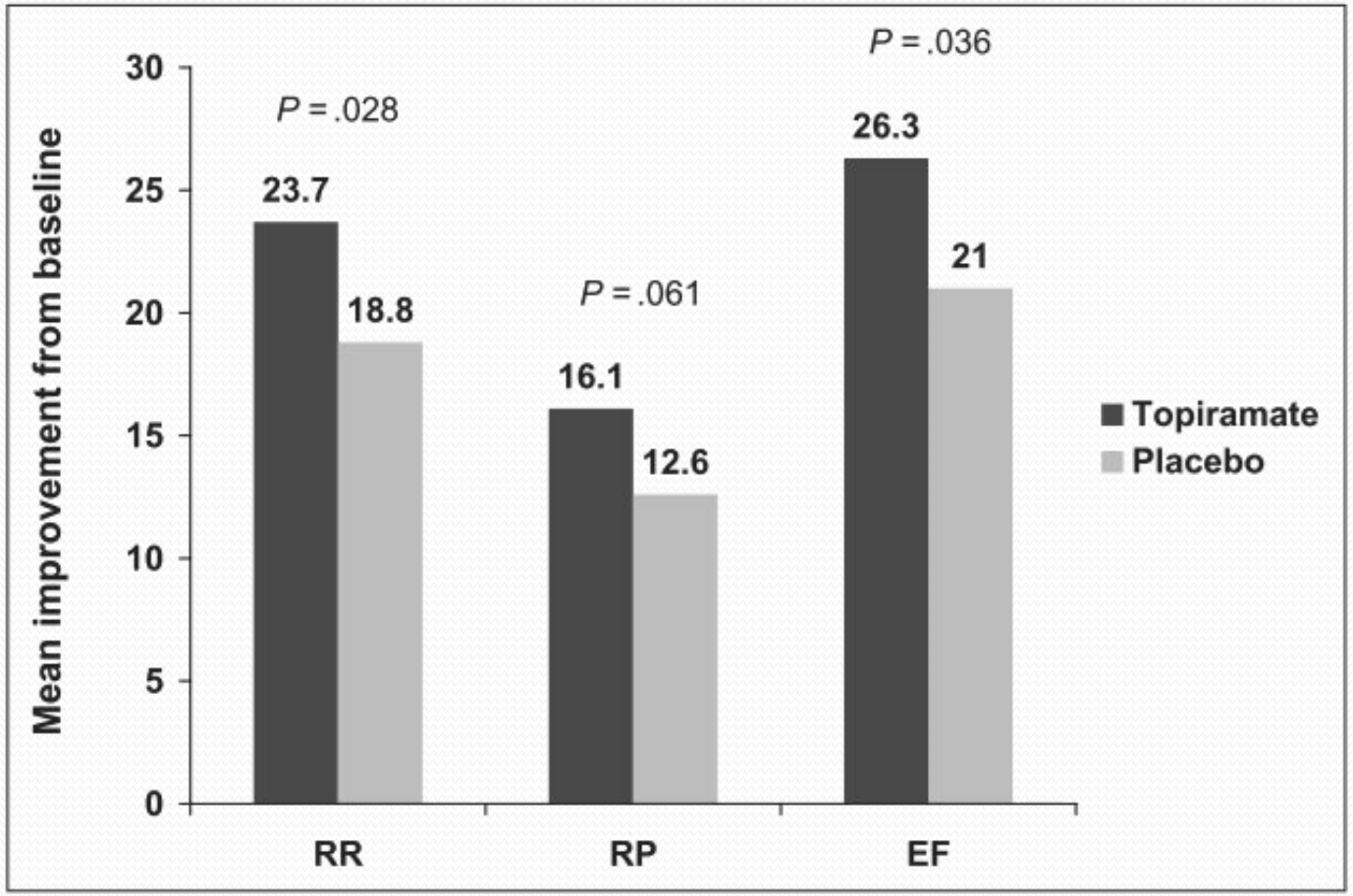
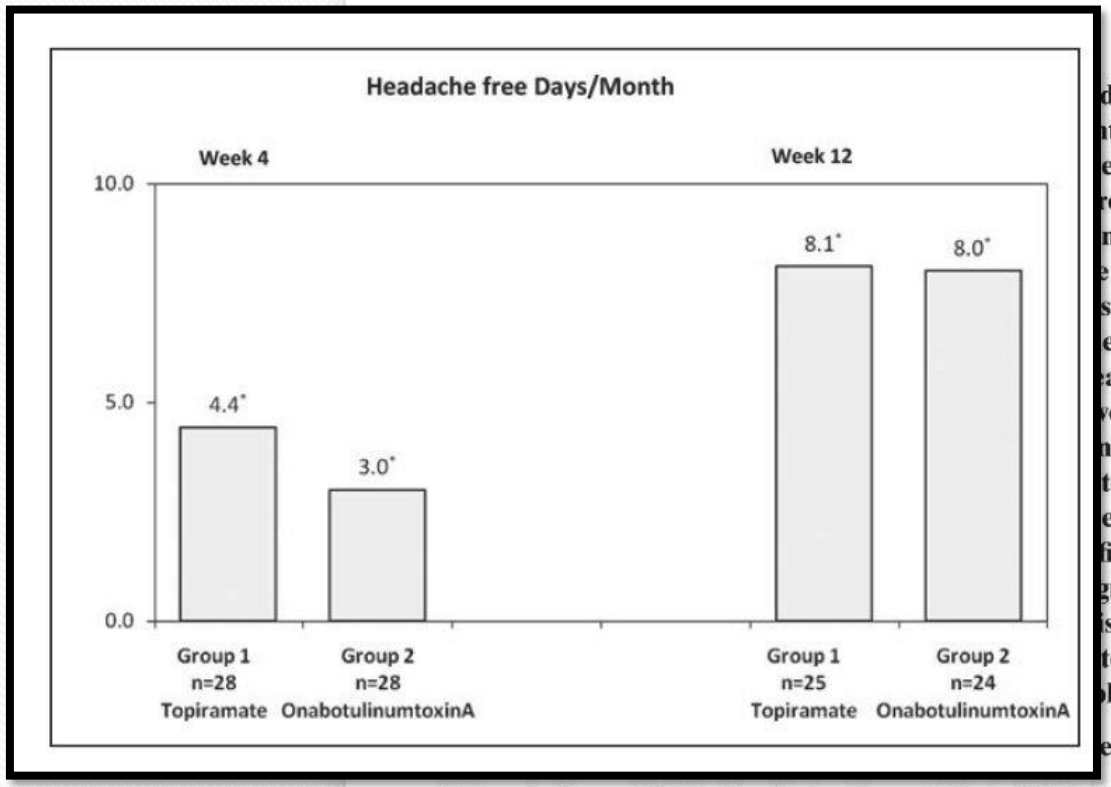


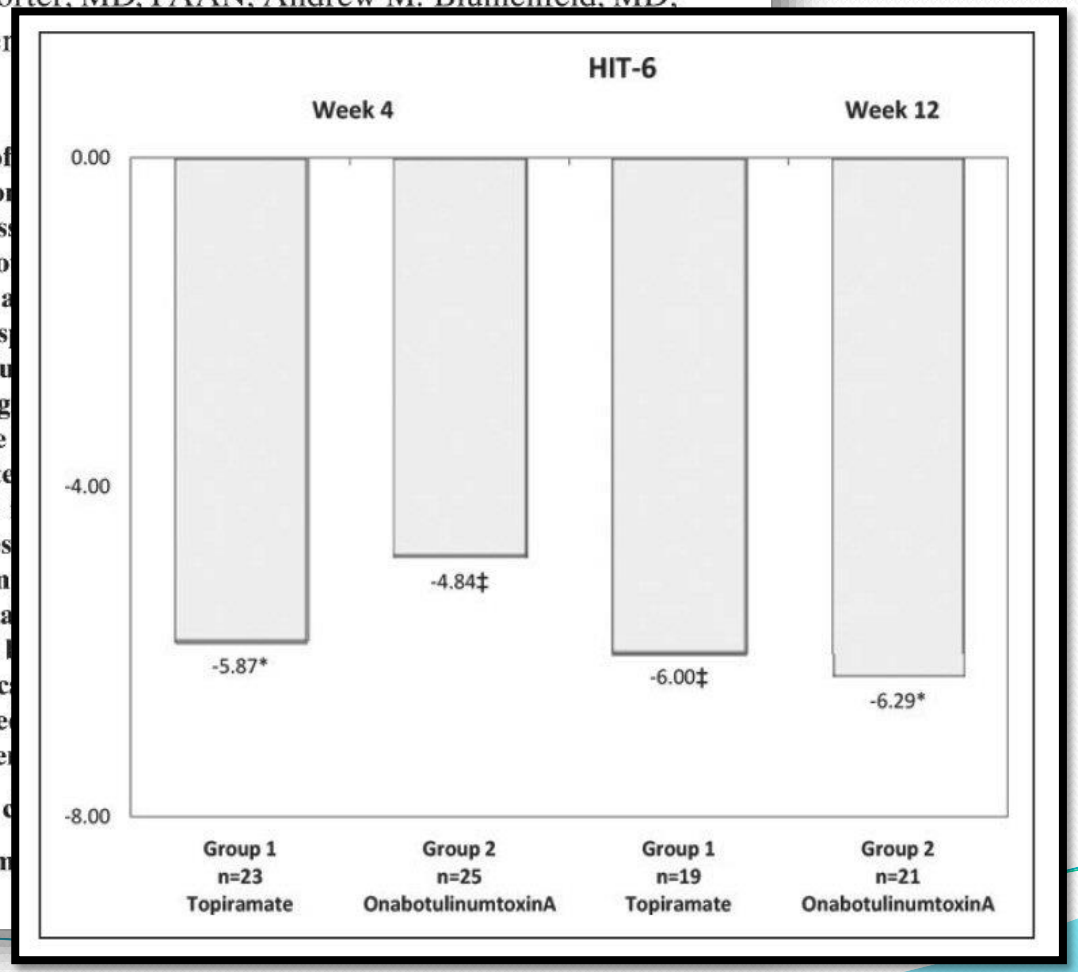
Fig 2.—Migraine-Specific Quality of Life Questionnaire (MSQ) results: mean change from baseline. An increase from baseline indicates improvement: intent-to-treat subjects. Changes from baseline to the final evaluations in scores on each MSQ domain Role Function-Restrictive (RR), Role Function-Preventive (RP), and Emotional Function (EF) were analyzed separately using the analysis of covariance model, with treatment and center as qualitative independent factors and baseline value as a covariate.

Headache 2009;49:1153-1162

A Multi-Center Double-Blind Pilot Comparison of OnabotulinumtoxinA and Topiramate for the Prophylactic Treatment of Chronic Migraine

Roger K. Cady, MD; Curtis P. Schreiber, MD; John A.H. Porter, MD, FAAN; Andrew M. Blumenfeld, MD; Kathleen U. Farmer



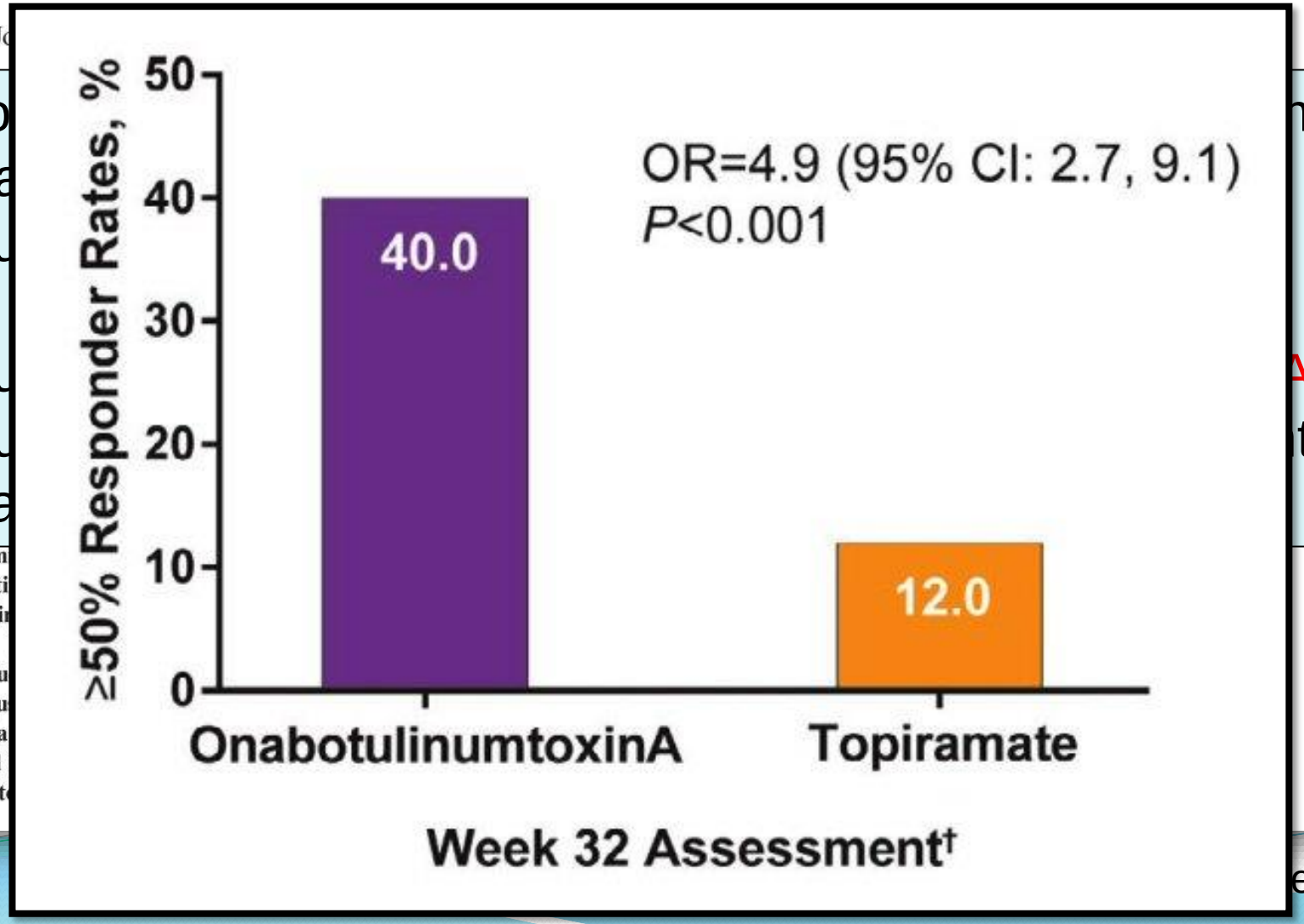


Abbreviations: HIT-6 Headache Impact Test, MIDAS Migraine Im… Questionnaire

Headache 2011;51:21-32

FORWARD Study: Evaluating the Comparative Effectiveness of OnabotulinumtoxinA and Topiramate for Headache Prevention in Adults With Chronic Migraine

We enro … nate,
n=142) a …
(onabotu …
Primary …
(onabotu … AEs
(onabotu … ty
topirama …



… e 2019;59:1700-13

Injectable MABs to CGRP or its Receptor: 3 Now FDA-Approved and Available

Terms: n=neurologic; umab=fully human; zumab=humanized, 90-95% human

	Erenumab-aooe (fully human)	Galcanezumab-gnlm (90% humanized)	Fremanezumab-vfrm (95% humanized)	Eptinezumab (90% humanized)
Studied for	EM, CM	EM, CM, eCH, cCH	EM, CM, eCH, cCH	EM, CM
Dosing	Monthly SC 70, 140 mg	Monthly SC; Load with 240 mg, then 120 mg SC monthly thereafter	Monthly or quarterly SC; 225 mg monthly, or 675 mg quarterly	Q3 month IV
Target	CGRP receptor	CGRP peptide or ligand	CGRP peptide or ligand	CGRP peptide or ligand
Regulatory status November 2018	**FDA approved 5/17/18 for migraine prevention**	**FDA approved 9/26/18 for migraine prevention (+ for eCH prevention but not yet submitted, - for cCH)**	**FDA approved 9/14/18 for migraine prevention (- for cCH)**	**FDA approved 2/21/20 for migraine prevention**

EM=episodic migraine. CM=chronic migraine. eCH= episodic cluster headache. cCH=chronic cluster headache.
1. Tepper SJ. *Headache* 2018;58:238-275. 2. Tepper SJ. *Headache* 2018;58:276-290.

Curtesy of Dr. Tepper

Box 5 | Drug prophylaxis of chronic migraine*

Highest level evidence (≥2 randomized placebo controlled trials)

Topiramate
OnabotulinumtoxinA

CGRP MAbs

Lower quality evidence (1 randomized study)

Sodium valproate
Gabapentin
Tizanidine
Amitriptyline

Lowest quality evidence (open label study)

Atenolol
Memantine
Pregabalin
Zonisamide

*The drugs listed have been studied specifically for prophylaxis in chronic migraine. However, drugs used for prophylaxis of episodic migraine are often used in chronic migraine, even in the absence of data supporting their use in this context.

BMJ 2014;348:g1416

藥物種類（建議劑量 mg/d）	在頭痛預防治療中的注意事項	證據強度	推薦等級
肉毒桿菌素 Botulinum toxin Type A		A	I
抗癲癇藥物 Anti-epileptic drug	Topiramate 注意肢端麻木、認知障礙與體重減輕等副作用。 Valproate 需注意肝功能，水腫、肥胖、掉髮等副作用。		
Topiramate (50-200)		B	I
Divalproex/valproate (300-1500)		C	III
Gabapentin (600-2400)		C	III
Levitiracetam (1000-3000)		C	III
鈣離子阻斷劑 Calcium channel blockers	Flunarizine 在老年人須注意錐體束外症候群副作用。		
Flunarizine (5-10)		B	II
抗憂鬱劑 Anti-depressants	其他之 TCA, SSRI, SNRI 抗憂鬱劑用於慢性偏頭痛療效尚未證實。		
Amitriptyline (10-75)		C	II
Fluoxetin (20-40)		C	III
其他類 Others			
Tizanidine (2-24)	在老年人須注意無力、跌倒等副作用。	C	III
Acupuncture	針刺部位、範圍、深度及時間尚無法標準化，端視個人之接受度	C	III

CGRP MAbs

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Adherence to oral migraine-preventive medications among patients with chronic migraine

Cephalalgia
2015, Vol. 35(6) 478–488

DOI: 10.1177/0333102414547138
cep.sagepub.com
SAGE

Results: Of the 75,870 patients identified with CM, 8688 met the inclusion/exclusion criteria. Adherence ranged between 26% to 29% at six months and 17% to 20% at 12 months depending on the calculation used to classify adherence (PDC and MPR, respectively). Adherence among the 14 OMPMs was similar except for amitriptyline, nortriptyline, gabapentin, and divalproex, which had significantly lower odds of adherence when compared to topiramate.
Conclusion: Adherence to OMPMs is low among the US CM population at six months and worsens by 12 months.

and MPR, respectively). Adherence among the 14 OMPMs was similar except for amitriptyline, nortriptyline, gabapentin, and divalproex, which had significantly lower odds of adherence when compared to topiramate.
Conclusion: Adherence to OMPMs is low among the US CM population at six months and worsens by 12 months.

Cephalalgia.2015;35,478-88

New Treatment of Chronic Migraine (CM) in Clinical practice

嘉義基督教醫院 神經內科

許永居主任

109/09/06

Learning points

1. Unmet Needs of Treatment Gap in CM
2. Botox Tx for Headache
3. Clinical Trials of Botox
   - PREEMPT
   - COMPEL
   - Forward
4. CGRP Antagonist
5. Botox for CM健保規範

Core messages

1

1. Unmet Needs of Treatment Gap in CM

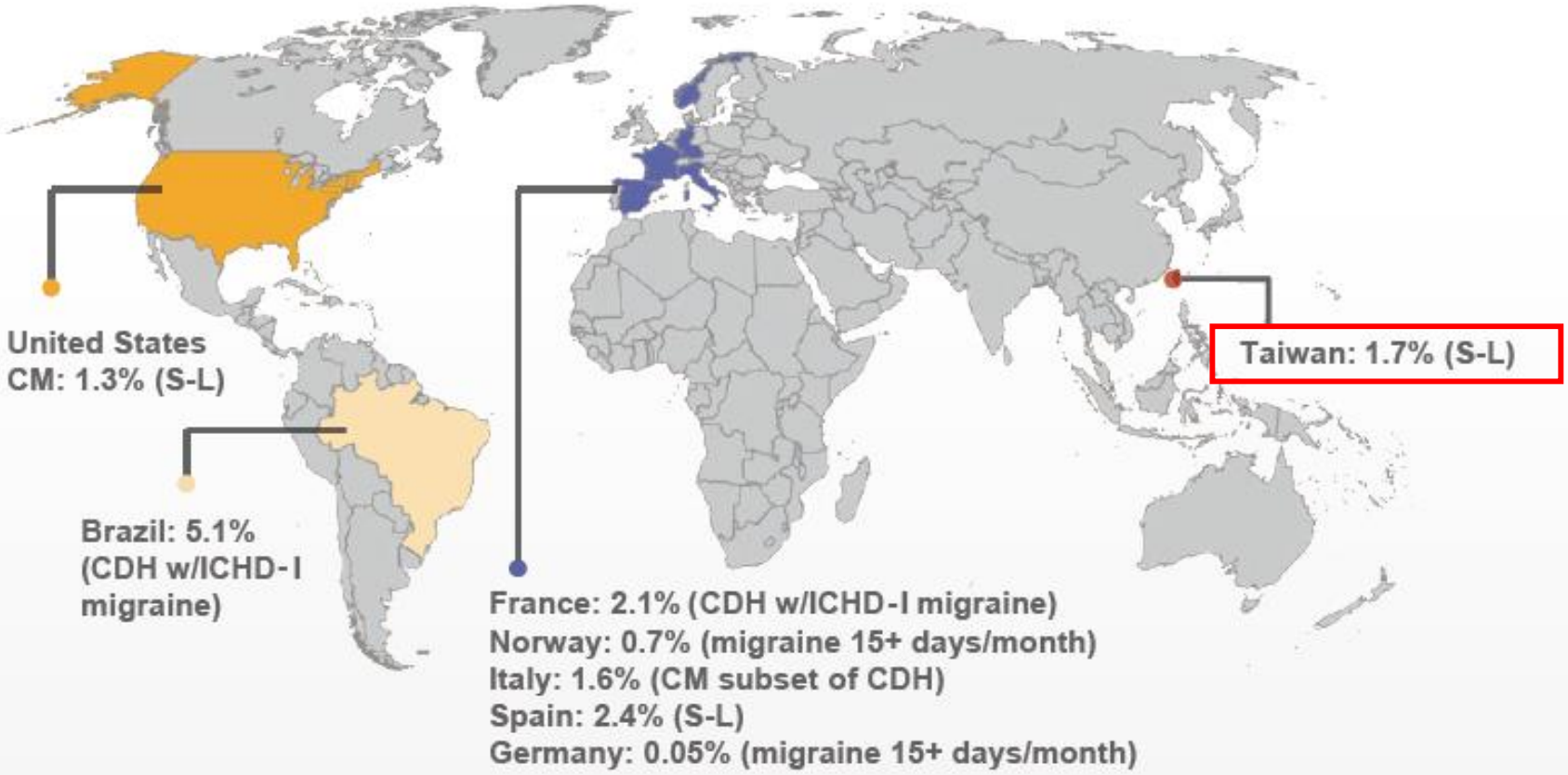
Description of chronic migraine

*does not specify consecutive

It therefore makes it difficult to diagnose chronic migraine as in practice, physicians will not have a 12-month headache journal from patients[1]

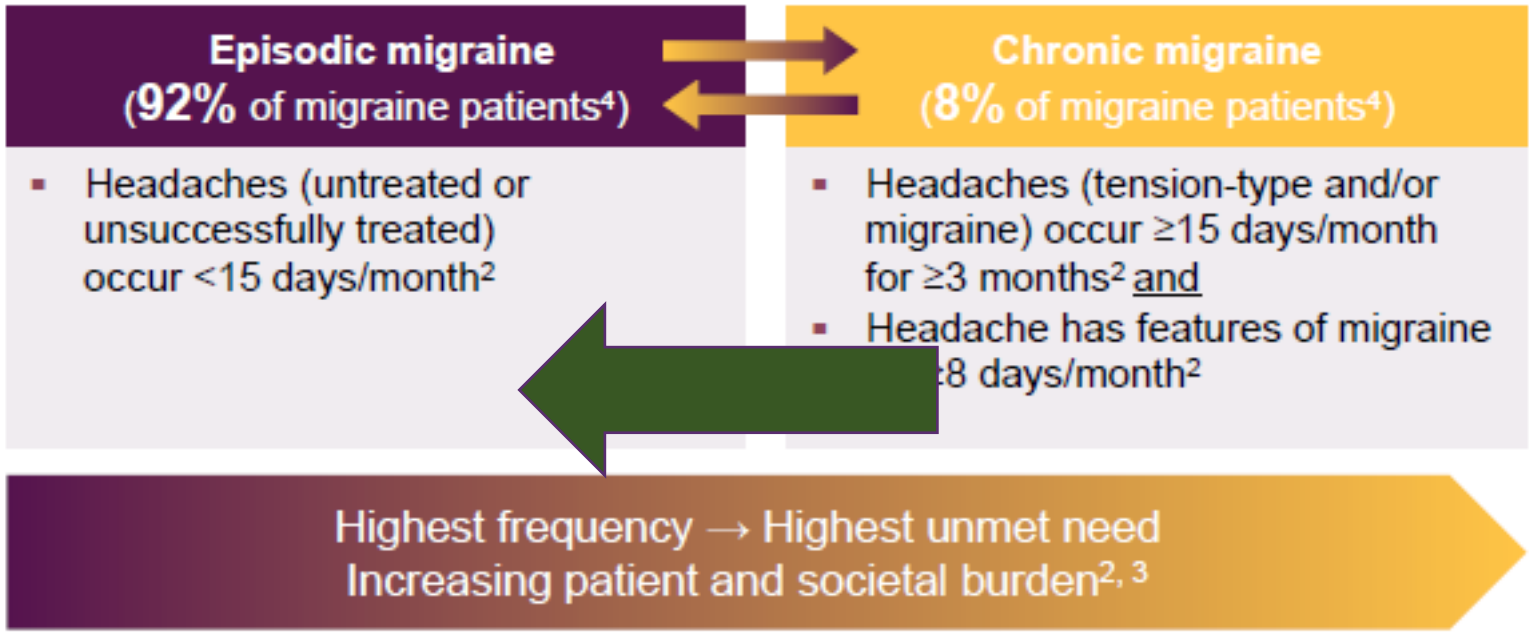
全球有高達2%的人口長期受到慢性偏頭痛的困擾[1]

- Chronic Migraines Definition:
- Headaches ≥ 15 days per month
- Migraines ≥ 8 days per month
- For > 3 months

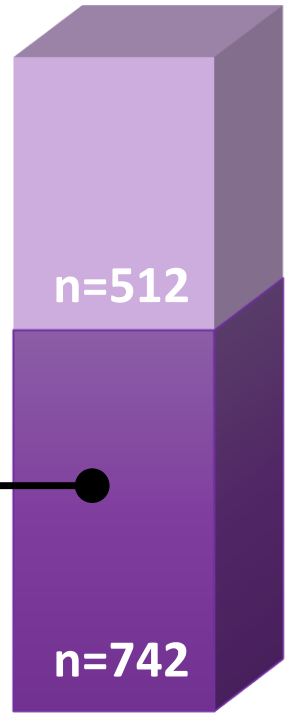


Classification of migraines as episodic or chronic depends on attack frequency[1, 2]

- A frequency score of ≥15 days/month is often used to differentiate between EM and CM[2]

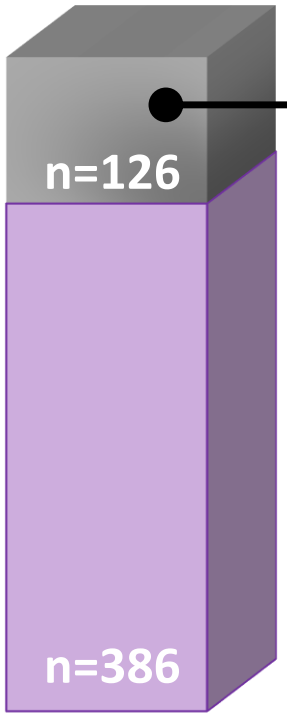


Many patients with chronic migraine remain undiagnosed



59.2%[1]

of chronic migraine patients eligible for analysis were **not** seeing a doctor or headache specialist about their headache



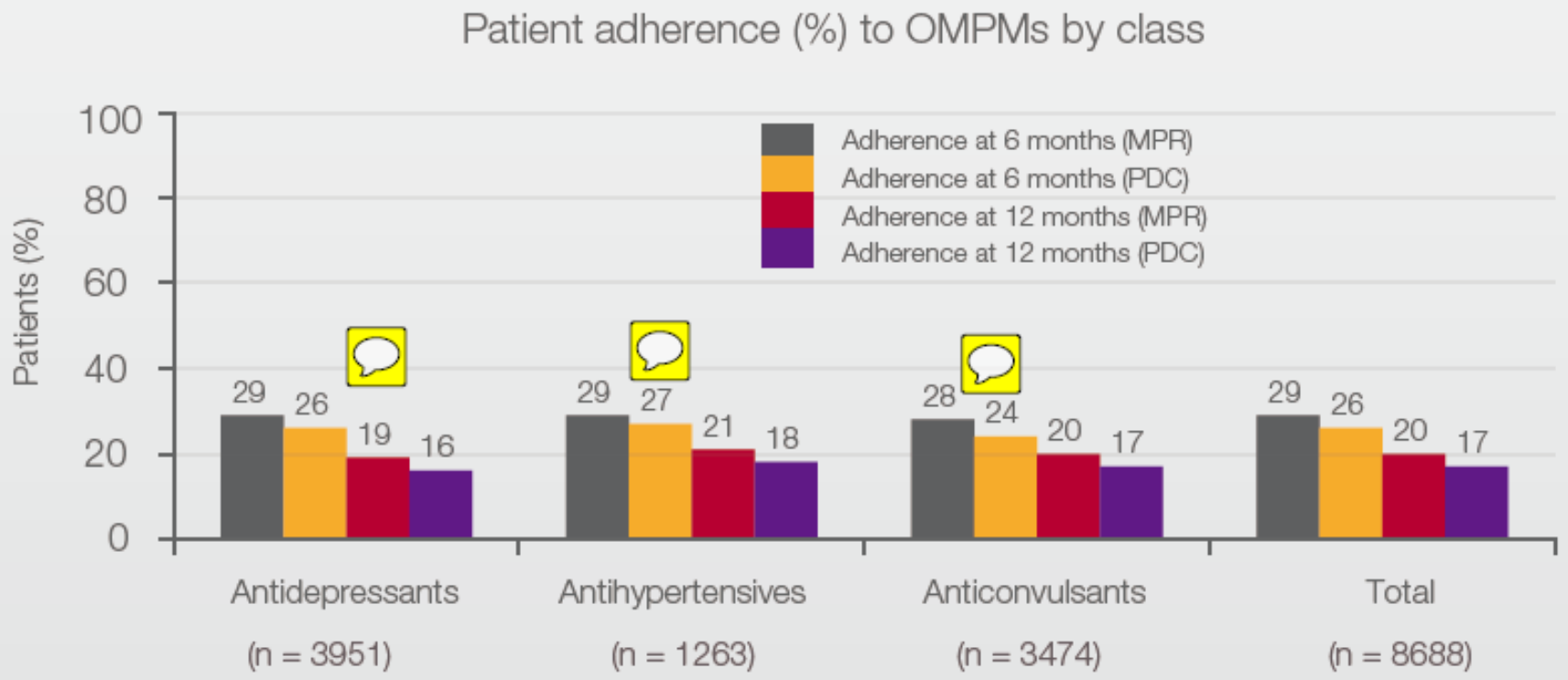
only

24.6%[1]

received a chronic migraine diagnosis despite meeting the criteria

1.Dodick DW, Headache. 2016. doi: 10.1111/head.12774.

多數口服預防性的藥物並無法被患者持續使用進而有效控制慢性偏頭痛[2]



MPR = (total number of days' supply)/(follow-up period);
PDC = (total number of days drug is available)/(follow-up period);
MPR, medication possession ratio;
OMPM, oral migraine-preventive medication;
PDC, proportion of days covered.

Preventive medications for chronic migraine

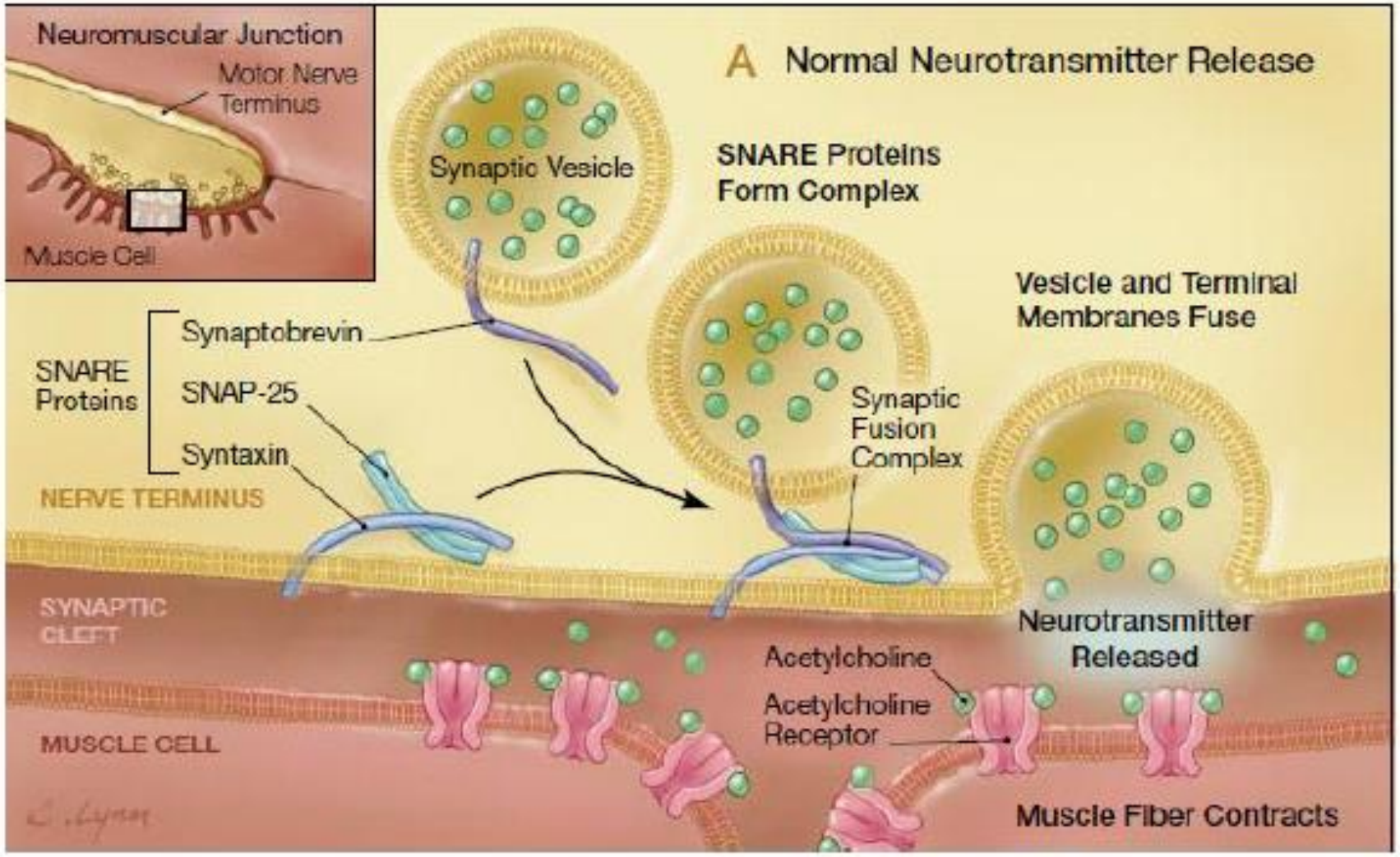
A	B	C	D
Antiepileptics	β-blockers	Ca^{2+} channel blockers	antidepressants
• Topiramate • Valproate • Gabapentin	• Propranolol • Atenolol • Metoprolol BoNTA	• Flunarizine • Verapamil CGRP Antagonist	• Amitriptyline • Nortriptyline • Venlafaxine

DB-PC Trials in chronic migraine: BoNTA, Topiramate, CGRP Antagonist

2

2. Botox Treatment for Headache

Botulinum toxin



SNARE: soluble NSF-attachment protein receptor; NSF: N-ethylmaleimide-sensitive fusion protein; SNAP-25: synaptosome-associated protein of 25kD

JAMA 2001; 285: 1059-70

Three methods of administration of BTX

A fixed site approach

Follow the Pain

A combination approach

Clinical data on botulinum toxin in patients with Episodic Tension-Type headache

Table 1. *Controlled studies on botulinum toxin in patients with tension-type headache*

Refs.	No. of patients	Dose [units]; distribution; formulation of BoNT/A	Rating of study (evidence class)	Result*	SAE
Rollnik et al. (2000)	21	200; FS; Dysport®	II	–	0
Schmitt et al. (2001)	60	20; FS; Botox®	II	–	0
Padberg et al. (2004)	40	100; FTP; Botox®	I	–	0
Schulte-Mattler et al. (2004)	112	500; FS; Dysport®	I	–	0
Silberstein et al. (2006)	300	50, 86, 100, 150; FS; Botox®	I	–	0

FTP Variable injection sites, "follow the pain approach"; *FS* fixed injection sites.

SAE Number of patients in that study with any serious adverse event related to botulinum toxin treatment.

* Results were judged as positive (+) only if the prospectively defined efficacy criterion was met.

J Neural Transm (2008) 115: 647–651

Clinical data on botulinum toxin in patients with CTTH

Table 1 Randomized, double-blind, placebo-controlled studies on botulinum toxin in the prophylactic treatment of tension-type headache

Study	Indication to treatment	Patients, *n*	Results compared with placebo
Göbel *et al.* (1999) [8]	Chronic tension-type headache	10	No significant reduction of pain intensity, headache hours, or use of analgesics
Smuts *et al.* (1999) [9]	Chronic tension-type headache	41	Significant reduction of headache intensity and pain-free days in month 3 compared with baseline data in group with botulinum toxin but not in placebo group
Rollnik *et al.* (2000) [10]	Chronic tension-type headache	21	No significant differences between botulinum toxin and placebo in any headache parameters
Burch *et al.* (2001) [11]	Episodic and chronic tension-type headache	41	No significant difference in headache frequency
Schmitt *et al.* (2001) [12]	Chronic tension-type headache	59	No significant differences between botulinum toxin and placebo in any headache parameters
Schulte-Mattler and Krack (2004) [13]	Chronic tension-type headache	113	No significant reduction in any efficacy endpoints
Kokoska *et al.* (2004) [14]	Chronic tension-type headache	40	No significant reduction of headache frequency; significant reduction of pain intensity
Padberg *et al.* (2004) [15]	Chronic tension-type headache	40	No significant results
Empl *et al.* (2005) [16]	Chronic tension-type headache	125	No significant results
Silberstein *et al.* (2006) [17]	Chronic tension-type headache	300	No significant difference in headache frequency (primary endpoint) for any treatment groups (treatment with 150 U was significantly inferior to placebo); significant increase in percentage of responders for 3 treatment groups

Current Opinion in Neurology 2006, 19:310–315

Clinical data on botulinum toxin in patients with Episodic Migraine

Table 3. *Controlled studies on botulinum toxin in patients with migraine*

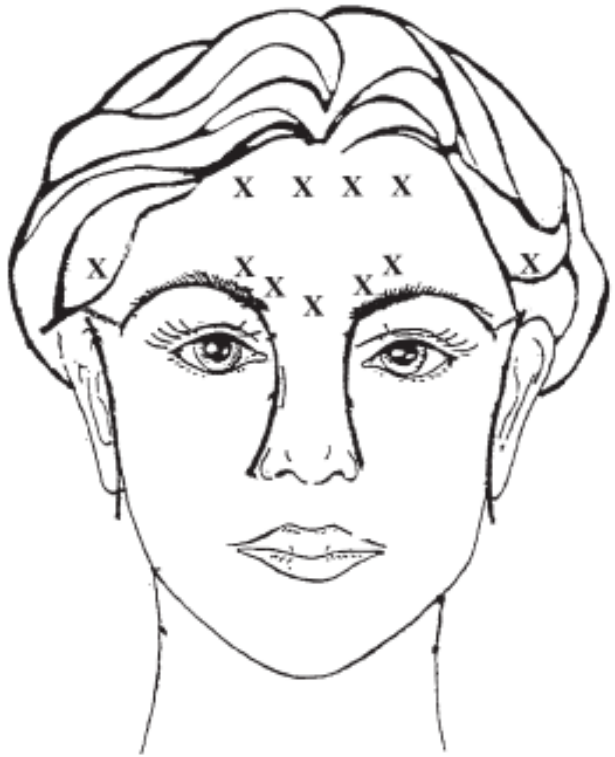
Refs.	No. of patients	Dose [units]; distribution; formulation of BoNT/A	Rating of study (evidence class)	Result*	SAE
Silberstein et al. (2000)	123	25, 75; FS; Botox®	II	–**	0
Barrientos and Chana (2003)	30	50, FS; Botox®	III	–***	0
Evers et al. (2004)	60	16, 100; FS; Botox®	I	–	0
Elkind et al. (2006)	418	7.5, 25, 50; FS; Botox®	II	–	0
Relja et al. (2007)	495	75, 150, 225; FS; Botox®	I	–	0
Aurora et al. (2007)	369	110–260; FTP; Botox®	I	–	0

FTP Variable injection sites, "follow the pain approach"; *FS* fixed injection sites.
SAE Number of patients in that study with any serious adverse event related to botulinum toxin treatment.
* Results were judged as positive (+) only if the prospectively defined efficacy criterion was met.
** Significant effect only in the 25 U group but not in the 75 U group.
*** No outcome criterion was defined prospectively.

J Neural Transm (2008) 115: 647–651

Botulinum Toxin Type A as a Migraine Preventive Treatment

Stephen Silberstein, MD; Ninan Mathew, MD; Joel Saper, MD; Stephen Jenkins, MD; for the BOTOX® Migraine Clinical Research Group



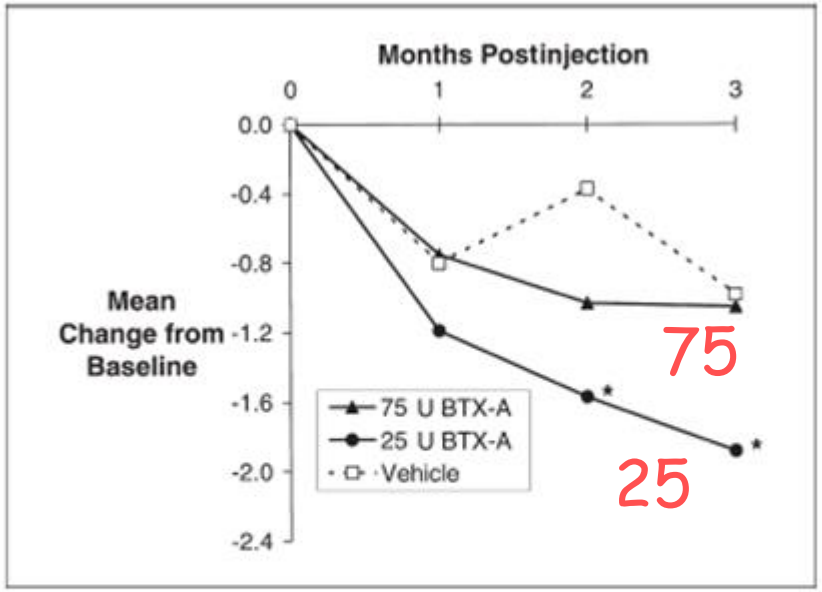


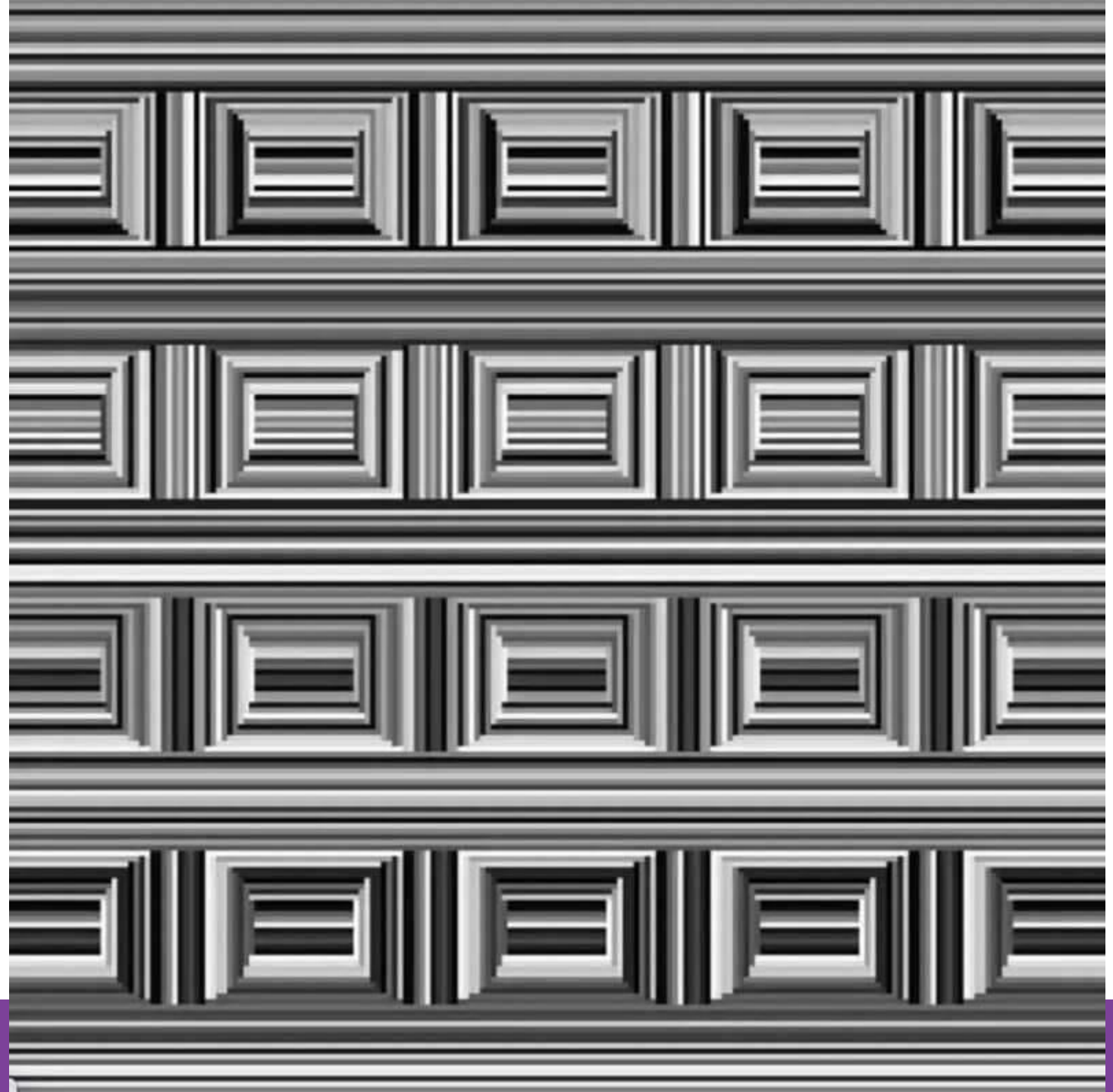
Fig 2.—Mean decrease from baseline in the number of moderate-to-severe migraines per month. Asterisks indicate that the 25-U BTX-A group was significantly different from the vehicle group at 2 and 3 months postinjection ($P \leq .042$).

Headache 2000;40:445-450

Clinical data on botulinum toxin in patients with Chronic Daily Headache

Table 3 Randomized, double-blind, placebo-controlled studies on botulinum toxin in the prophylactic treatment of chronic daily headache

Study	Indication to treatment	Patients, *n*	Results compared with placebo
Ondo *et al.* (2004) [41]	Chronic daily headache	60	No significant reduction but trend (P 0.07) in primary endpoint (days with headache)
Silberstein *et al.* (2005) [42•]	Chronic daily headache	702	No significant reduction of headache frequency
Mathew *et al.* (2005) [43•]	Chronic daily headache	355	Primary endpoint (reduction of headache-free days) negative; secondary endpoint (percentage of patients with reduction > 50%) positive
Dodick *et al.* (2005) [44•]	Chronic daily headache	228	Significant reduction of headache frequency in patients not receiving other prophylactic drugs (subanalysis of study [43•])
Elkind and Turkel (2005) [45]	Chronic migraine	355	Significant reduction of migraine frequency for all treatment arms (105–260 U Botox; Allergan, Inc., Irvine, CA, USA) as compared with placebo (subanalysis of study [43•])



2010 PREEMPT

3-1

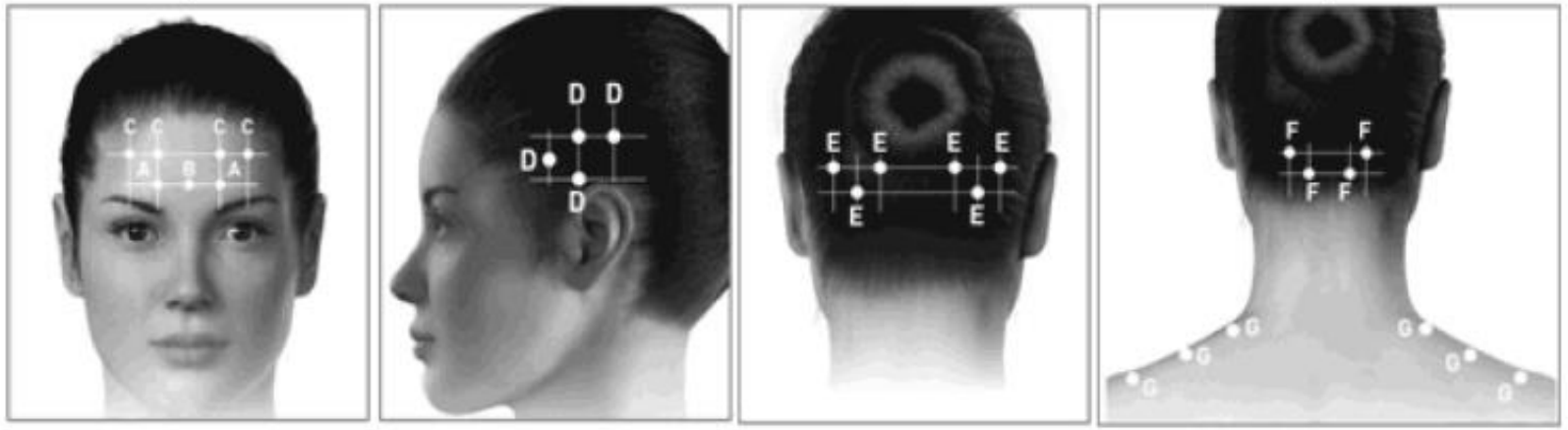
Clinical trials: PREEMPT

先發制人

Based on evidence, Botox Tx only for CM

The fixed-site, fixed-dose injection paradigm

- A total of 31−39 injections across seven specific head and neck muscles, with a minimum dose of 155 U BOTOX® per patient and a maximum dose of 195 U of BOTOX® using the ‘follow the pain’ method[1]
- Administered every 12 weeks[2]



A Corrugator **5 U each side**	D Temporalis **20 U each side**	E Occipitalis **15 U each side**	F Cervical paraspinal **10 U each side**
B Procerus **5 U each (one side)**			G Trapezius **15 U each side**
C Frontalis **10 U each side**			

Adapted from BOTOX® SmPC[2]

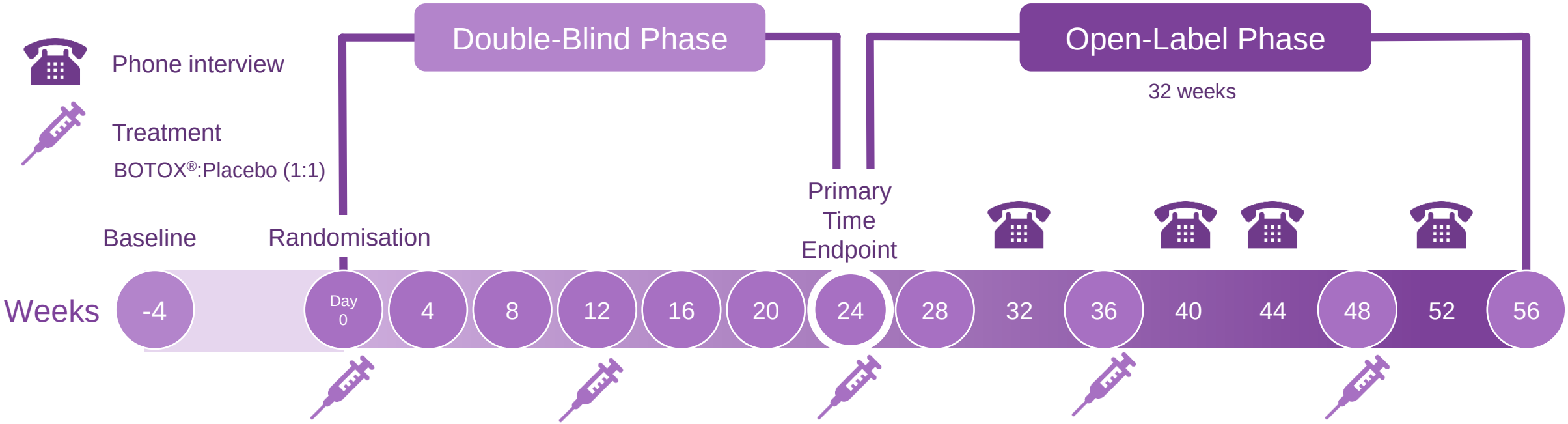
1. Blumenfeld A, et al. Headache 2010;50:1406–18.
2. BOTOX ® Summary of Product Characteristics March 2019.

2/3 MOH, 2/3 Oral Preventive Tx failure

PREEMPT study overview

Onabotulinumtoxin A for treatment of chronic migraine: Pooled results from the double-blind, randomised, placebo-controlled phases of the PREEMPT clinical programme[1]

Design
Pooled results of two randomised, placebo-controlled, double-blind, Phase 3 studies[1]



Adapted from Dodick DW, et al. 2010.

1. Dodick DW, et al. Headache. 2010;50:921–936.

PREEMPT study overview

Onabotulinumtoxin A for treatment of chronic migraine: Pooled results from the double-blind, randomised, placebo-controlled phases of the PREEMPT clinical programme[1]

Design

Pooled results of two randomised, placebo-controlled, double-blind, Phase 3 studies

Number of patients (N)

1,384 patients were included in this analysis (placebo, n=696; BOTOX®, n=688)

Key inclusion criteria

- Aged 18–65 years with a history of migraine
- Headache days ≥15 days per 28-day period lasting ≥4 hours per day of which ≥50% were migraine or probably migraine

Dosing/treatment arms

- 2 treatment cycles of 155 U BOTOX® administered every 12 weeks
- An additional 40 U BOTOX® could be administered using a "follow-the-pain" strategy

Key baseline parameters

- Mean headache days per month: Placebo, 19.8; BOTOX®, 19.9
- Mean moderate or severe headache days per month: Placebo, 18.0; BOTOX®, 18.1
- Mean HIT-6 total score: Placebo, 65.4; BOTOX®, 65.5

Primary endpoint

Headache days per 28-day period immediately before Week 24

Other endpoints

- Frequency of migraine/probable migraine days
- Frequency in moderate or severe headache days
- Proportion of patients with severe HIT-6 score (≥60 points)
- Frequency of headache episodes

1. Dodick DW, et al. Headache. 2010;50:921–936.

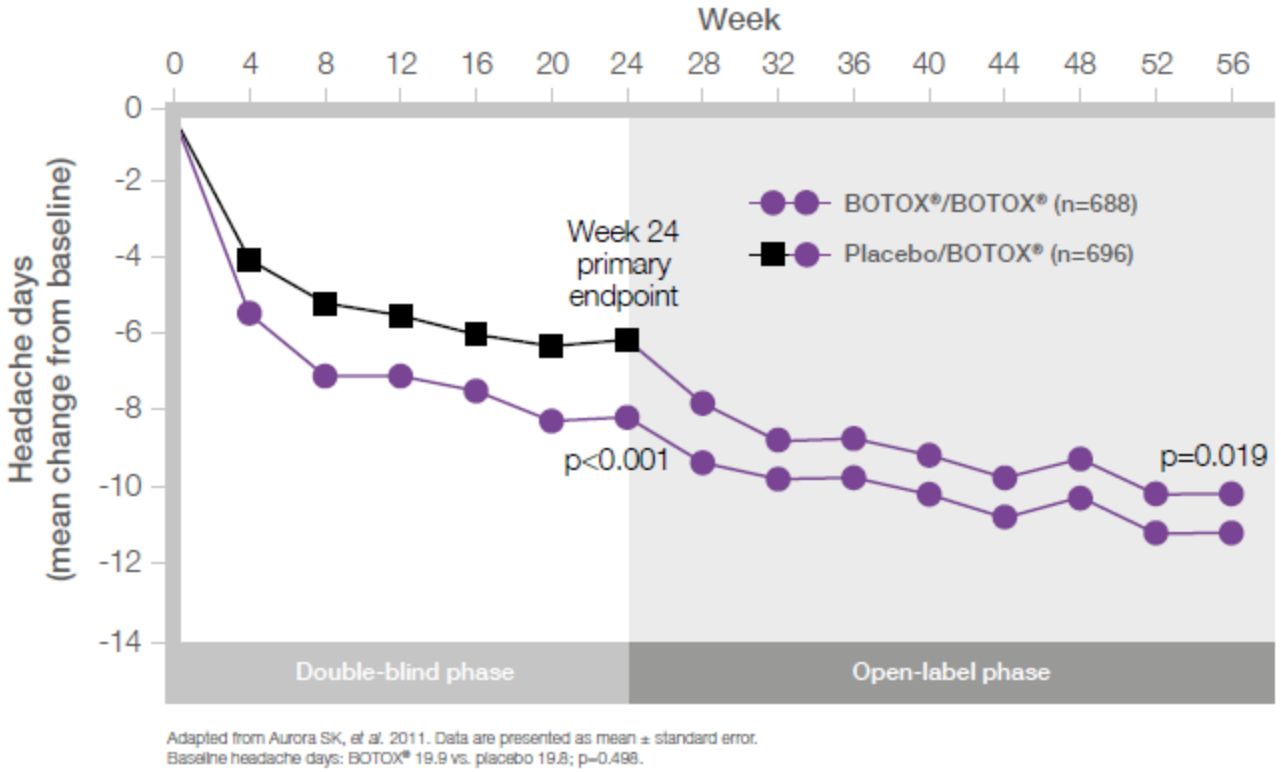
PREEMPT study endpoints

PREEMPT 1[1]	PREEMPT 2[2]	Pooled analysis[3]
Primary endpoints		
Frequency of headache episodes: • Mean change from baseline per 28-day period • Defined as headache pain lasting ≥4 continuous hours	Frequency of headache days: • Mean change from baseline per 28-day period • Defined as a calendar day (00:00 to 23:59) with ≥4 continuous hours of headache	Frequency of headache days: • Mean change from baseline per 28-day period • Defined as a calendar day (00:00 to 23:59) with ≥4 continuous hours of headache
Secondary endpoints		
Frequency of headache days	Frequency of migraine / probable migraine days	Frequency of migraine / probable migraine days
Frequency of migraine / probable migraine days	Frequency of moderate / severe headache days	Frequency of moderate / severe headache days
Frequency of migraine / probable migraine episodes	Total cumulative hours of headache on headache days	Total cumulative hours of headache on headache days
Frequency of acute headache pain medication intake	Proportion of patients with severe HIT-6 category scores (≥60)	Proportion of patients with severe HIT-6 category scores (≥60)
	Frequency of headache episodes	Frequency of headache episodes
		Frequency of migraine / probable migraine episodes
		Frequency of acute headache pain medication intake

1. Aurora SK, et al. Cephalalgia 2010;30:793–803.
2. Diener HC, et al. Cephalalgia 2010;30:804–14.
3. Dodick DW, et al. Headache 2010;50:921–36.

PREEMPT pooled analysis: Primary endpoint, frequency of headache days[1]

BOTOX® significant improvement in the frequency of headache days compared with placebo (p<0.001 at 24 weeks) was sustained to the end of the 56-week, open-label period (p=0.019)[2]



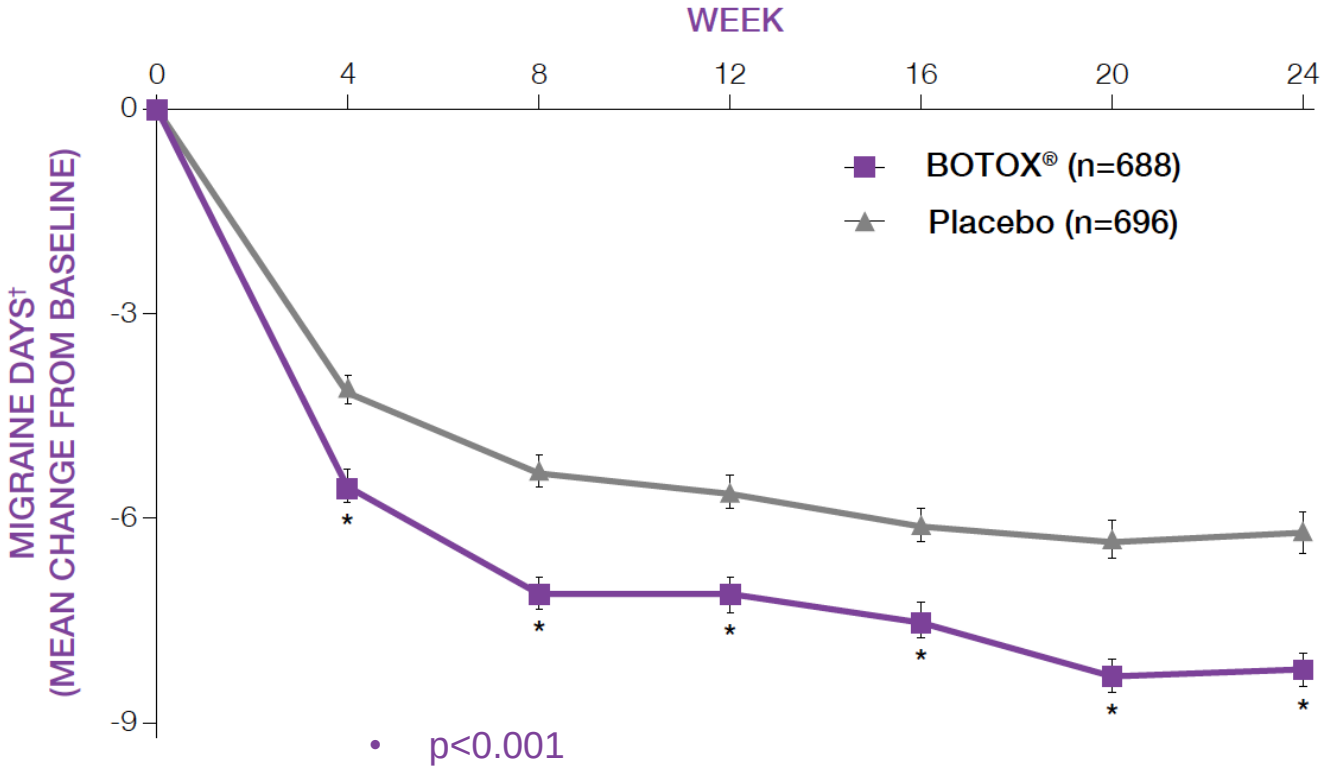
Adapted from Aurora SK, *et al.* 2011. Data are presented as mean ± standard error.
Baseline headache days: BOTOX® 19.9 vs. placebo 19.8; p=0.498.

Adapted from Aurora 2011

1. Dodick DW, et al. Headache 2010;50:921–36.
2. Aurora SK, et al. Headache 2011; 51 (9): 1358–73.

PREEMPT pooled analysis: Secondary endpoint, frequency of migraine days[1]

BOTOX® significantly reduced migraine days compared with placebo at every endpoint.[1]

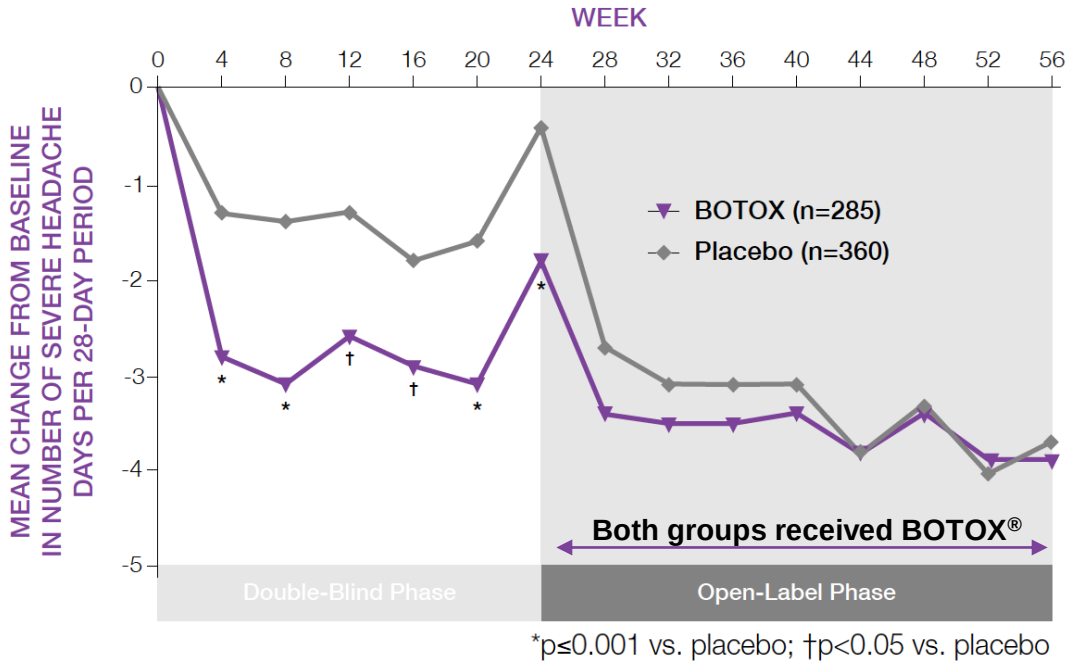


Adapted from Dodick 2010

1. Dodick DW, et al. Headache. 2010;50:921–936.

PREEMPT pooled analysis: Secondary endpoint, frequency of severe headache days in the non-responder group[1ŧ]

BOTOX® significantly reduced the number of severe headache days compared to placebo ($p<0.001$ at 24 weeks) and was sustained to the end of the 56-week, open-label period in the non-responder group ($p< 0.05$).[1]



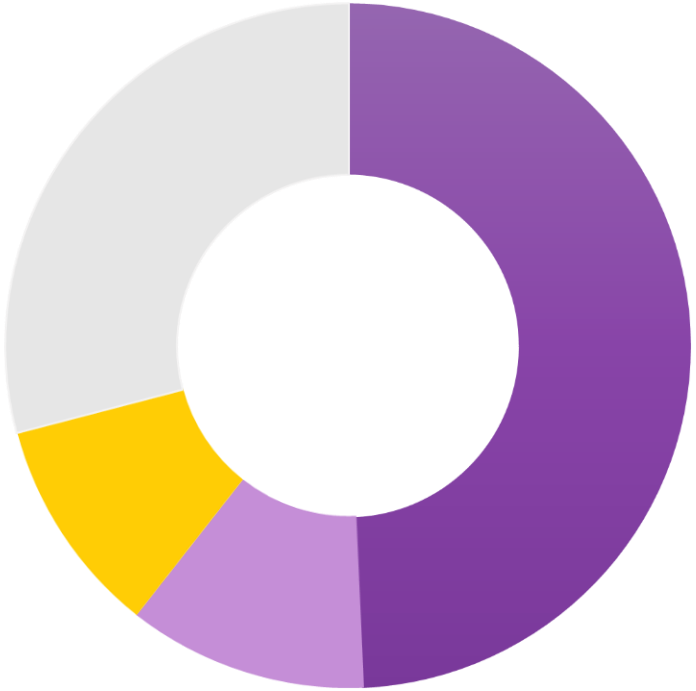
Adapted from Matharu M, et al. 2017.

1. Matharu M, *et al*. J Headache Pain. 2017;18(1):78.

ŧ A non-responder was defined as those that achieved <50% reduction in headache days

≥50% responder rates in the PREEMPT clinical trial

- Cumulative proportion of BOTOX®-treated patients responding with a ≥50% reduction in headache days in the PREEMPT trials with each treatment cycle[1]
- Re-treatment is recommended every 12 weeks[2]



- **49.3%** responded after the first treatment cycle (n=339)[1]
- **60.6%** responded after the second cycle (n=417)[1]
- **70.9%** responded after the third cycle (n=488)[1]

1. Silberstein SD, et al. J Neurol Neurosurg Psychiatry 2015; 86(9): 996–1001.
2. Summary of Product Characteristics. BOTOX®. Allergan Ltd, March 2019.

PREEMPT study safety results

- Pooled data confirmed the tolerability of BOTOX® as a prophylactic treatment for chronic migraine[1]
- The nature and frequency of adverse events were similar for both groups, and no new safety or tolerability events emerged from the pooled results in the double-blind phase[1]
- BOTOX®-treated patients experienced a greater number of adverse events than placebo-treated patients[1]
- The individual adverse events that occurred at a rate ≥5% in either group during the double-blind phase were neck pain (8.7%) and muscular weakness (5.5%) in the BOTOX® group (N=687) and upper respiratory tract infection (5.3%) in the placebo group (N=692)[1]
- During the double-blind phase, serious adverse events were reported in 4.8% (33/687) of patients receiving BOTOX® and 2.3% (16/692) of patients receiving placebo[1]

3.8% BOTOX®-treated patients discontinued due to AEs[1]

1. Dodick DW, et al. Headache. 2010;50:921–936.

PREEMPT study safety results

The rate of treatment-emergent adverse events progressively decreases with subsequent rounds of BOTOX® treatment[1]

Adverse events by treatment cycle for patients who received all five treatments of onabotulinumtoxin A[1]

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
Adverse event	N=513	N=513	N=513	N=513	N=513
Overall	248 (48.3%)	191 (37.2%)	194 (37.8%)	135 (26.3%)	98 (19.1%)

1. Aurora et al 2014, Acta Neurologica Scandinavica 129 (1) 61-70.

2-2

Clinical trials COMPEL

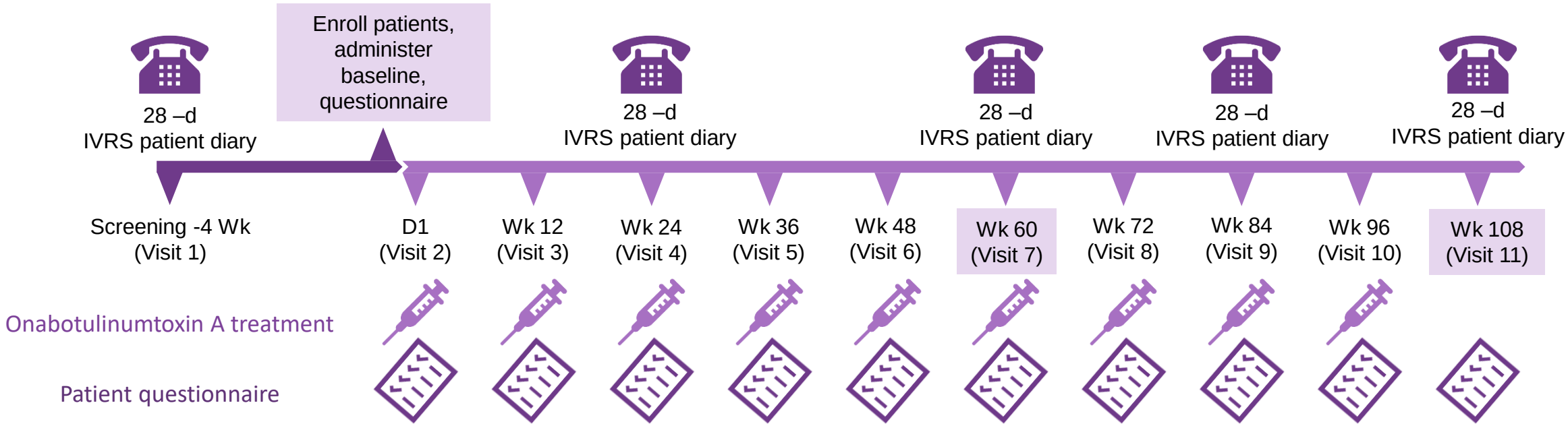
逼迫

COMPEL study overview

Long-term study of the efficacy and safety of Onabotulinumtoxin A for the prevention of chronic migraine: COMPEL study[1]

Design[1]

- International, multicentre, open-label, prospective trial
- To assess efficacy and safety of BOTOX® for 9 treatment cycles in patients with chronic migraine



28-d: 28 days before reference visit; IVRS: Interactive voice response system.

Adapted from Blumfeld AM, et al. 2018.

1. Blumenfeld AM et al. J Headache Pain 2018;19(1):1.

COMPEL study overview

Long-term study of the efficacy and safety of Onabotulinumtoxin A for the prevention of chronic migraine: COMPEL study[1]

Design[1]
- International, multicentre, open-label, prospective trial
- To assess efficacy and safety of BOTOX® for 9 treatment cycles in patients with chronic migraine

Number of patients (N)[1]
- 716 enrolled; 373 completed the study

Key inclusion criteria[2]
- Aged ≥18 years with a diagnosis of chronic migraine
- Headache days ≥15 days per month lasting ≥4 hours per day
- Patients could take a single oral medication as headache prevention

Dosing/treatment arms[1]
- 9 treatment cycles of 155 U BOTOX® administered every 12 weeks

Key baseline parameters[2]
- Mean headache days per 28 days was 22
- Mean moderate or severe headache days per 28 days was 18
- Mean HIT-6 total score was 64.7

Primary endpoint[1,2]
Headache days per 28-day period immediately before Week 108

Exploratory outcome measures[1]
Change from baseline in:
- PHQ-9
- Generalised Anxiety Disorder (GAD-7)
- Pittsburgh Sleep Quality Index (PSQI)
- Fatigue Severity Scale (FSS) scores
- Safety and tolerability

1. Blumenfeld AM, *et al*. J Neurol Neurosurg Psychiatry. 2019;90(3):353–360. 2. Blumenfeld AM et al. J Headache Pain 2018;19(1):1.

COMPEL: Primary efficacy endpoint, headache frequency at 108 weeks[1]

Patients receiving BOTOX® experienced a significant reduction in the number of headache days per month from baseline (–10.7 days, p<0.0001; n=715), by 108 weeks.

*p<0.0001

Adapted from Blumenfeld AM, et al. 2018.

1. Blumenfeld AM et al. J Headache Pain 2018;19(1):1.

COMPEL: Exploratory outcomes

BOTOX® improved comorbid symptoms of depression and anxiety[1]

Clinically meaningful improvements from baseline with BOTOX® in comorbid depression symptoms and anxiety scores:[1]

- 61.8% and 69.3% at Week 12 (n=471)
- 78.0% and 81.5% at Week 108 (n=254)

In the CaMEO study:
1,476 people with chronic migraine:[2]

- 56% had comorbid depression
- 48% had generalised anxiety disorder

1. Blumenfeld AM, *et al*. J Neurol Neurosurg Psychiatry. 2019;90(3):353–360 . 2.Adams AM, et al. Cephalagia 2015;36(7):563–5.

COMPEL study safety results[1]

- 436 patients (60.9%) reported ≥1 treatment-emergent adverse event (TEAE)
- 131 patients (18.3%) reported ≥1 treatment-related adverse event (TRAE)
  - Neck pain was the most commonly reported TRAE (n=29, 4.1%)
- One patient reported a serious TRAE (rash)
- No deaths were reported

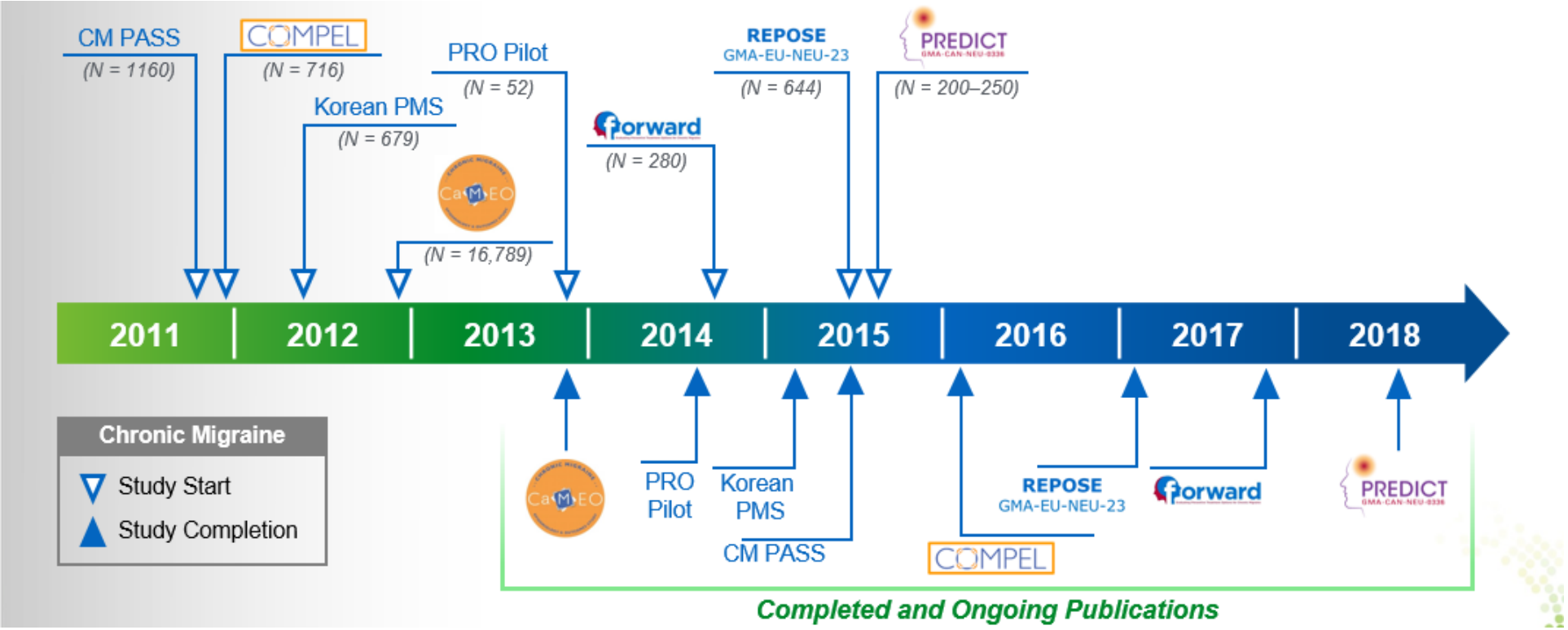
3.5% of BOTOX®-treated patients discontinued due to adverse events (n=32)[2]

Safety population (n=716)

Summary of TRAEs occurring in ≥1% of the study population	Overall (n=716)
TRAEs, n (%)	**131 (18.3)**
Neck pain	29 (4.1)
Eyelid ptosis	18 (2.5)
Musculoskeletal stiffness	17 (2.4)
Injection-site pain	14 (2.0)
Headache	12 (1.7)
Muscular weakness	10 (1.4)
Facial paresis	9 (1.3)
Migraine	7 (1.0)
Skin tightness	7 (1.0)

1. Blumenfeld AM et al. J Headache Pain 2018;19(1):13.
2. Blumenfeld AM, *et al*. J Neurol Neurosurg Psychiatry. 2019;90(3):353–360

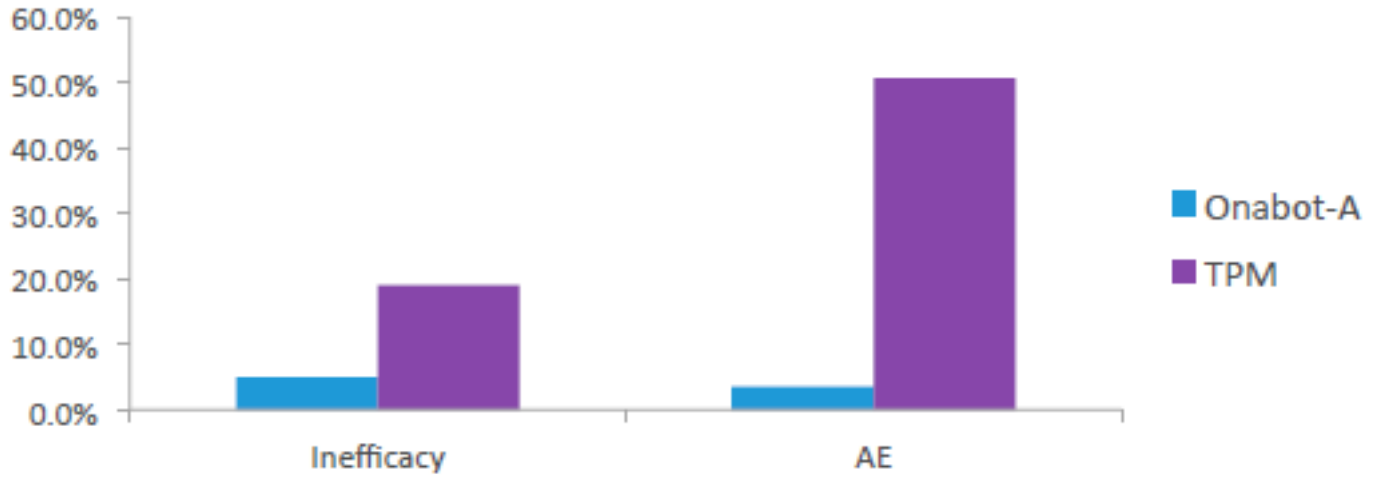
Continuous chronic migraine data generation



Allergan

FORWARD study

- A multicenter, Prospective, Randomized, Open-Label study
- Onabot-A X 3 cycles vs TPM 50-100 mg/day
- Discontinuation rate: Onabot-A 14.3%, TPM 80.3%



Blumenfeld, A. et al AHS 2018

4

CGRP Antagonist

Clinical trials of mAbs

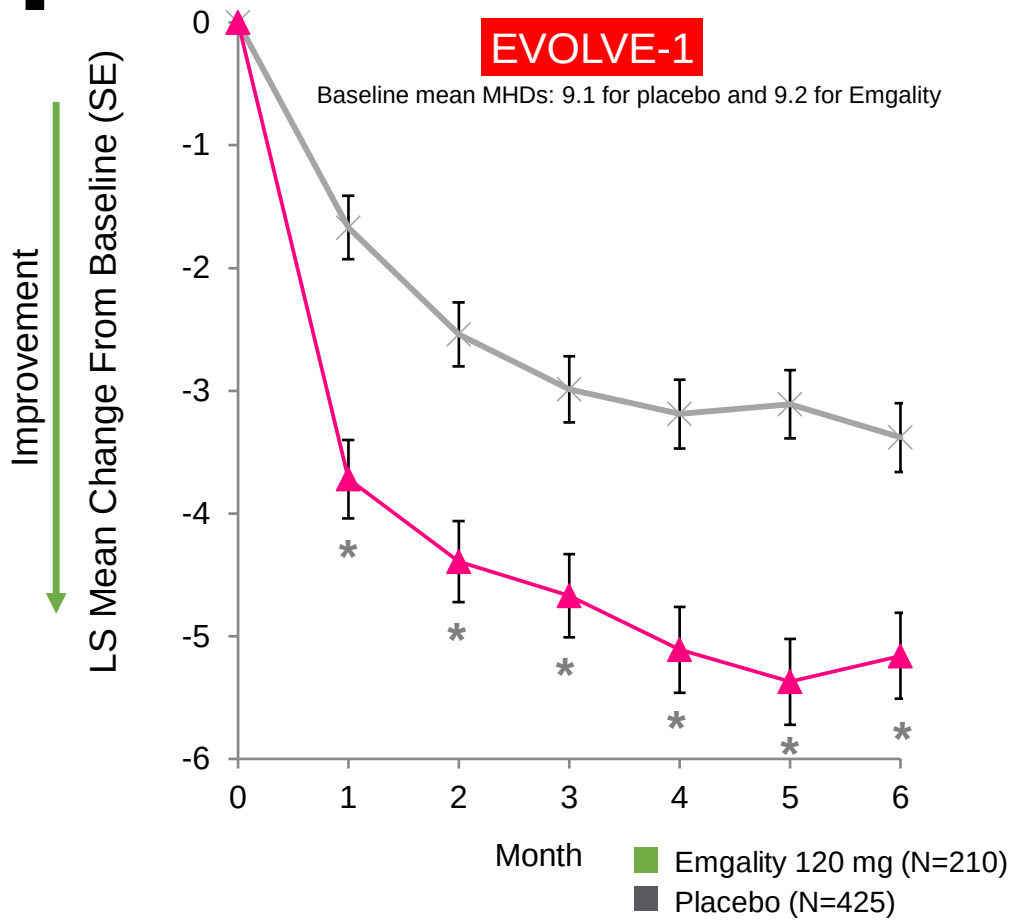
Emgality

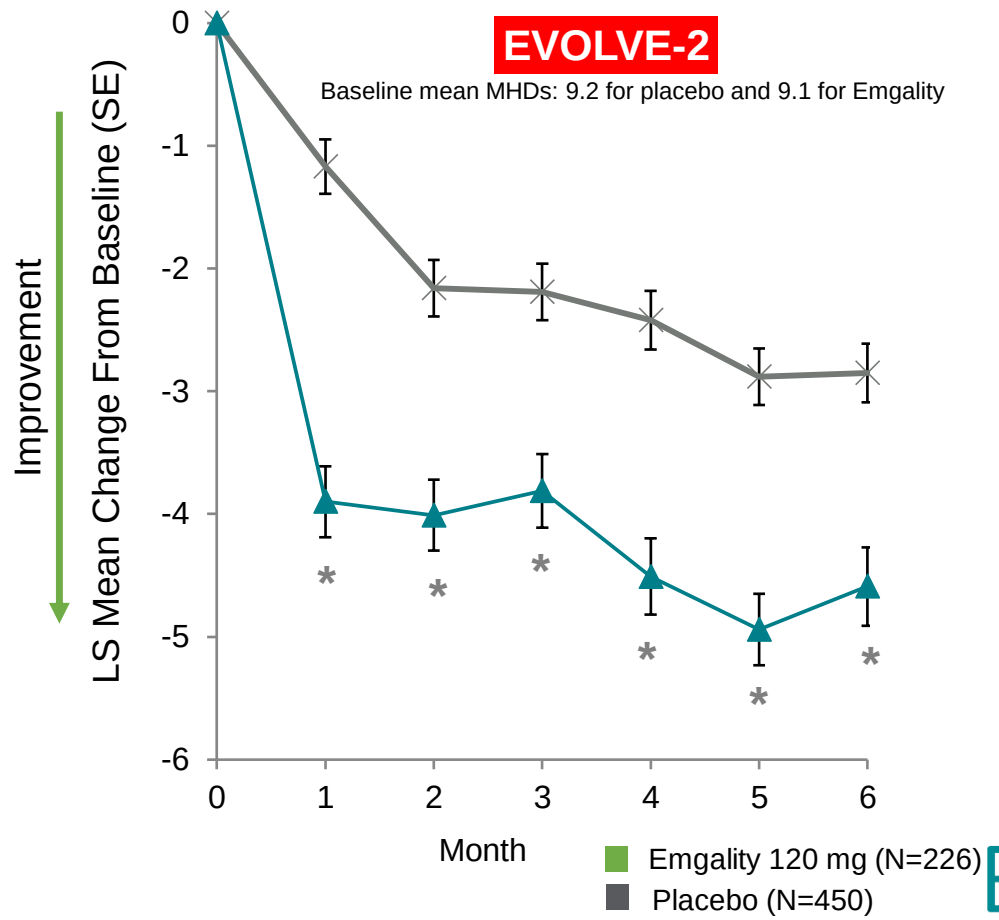
Drug	Episodic migraine	Chronic migraine
Galcanezumab	EVOLVE-1 (JAMA Neurol 2018;75:1080-8) EVOLVE-2 (Cephalalgia 2018;38:1442-54)	REGAIN (Neurology 2018;91:e2211-21)
Eptinezumab	PROMISE-1 (2018 AAN annual meeting)	PROMISE-2 (2019 AAN annual meeting)
Fremanezumab	HALO (JAMA 2018;319:1999-2008)	HALO (NEJM 2017;377:2113-22)
Erenumab	STRIVE (NEJM 2017;377:2123-32) ARISE (Cephalalgia 2018;38:1026-37)	(phase 2 trial) (Lan Neurol 2017;16:425-34)

EPISODIC MIGRAINE:

Change From Baseline in Mean Monthly Migraine Headache Days (MHDs)[1,2]

Emgality significantly reduced MHDs as early as Week 1 vs placebo† and also demonstrated significant reduction at Month 1 and each month therafter[1-3]





*p<0.001 vs. placebo

1. Stauffer VL, et al. *JAMA Neurol*. 2018;75(9):1080-1088. **2.** Skljarevski V, et al. *Cephalalgia*. 2018;38(8):1442-1454. **3.** Aurora SK, et al. Presented at: 60Th Annual Scientific Meeting of the American Headache Society: June 28-July 1, 2018: San Francisco, CA.

Emgality® (galcanezumab) injection

CHRONIC MIGRAINE: REGAIN

Emgality Demonstrated an Average Reduction of 4.8 Migraine Headache Days (MHDs) per Month vs 2.7 With Placebo ($p<0.001$)[1]

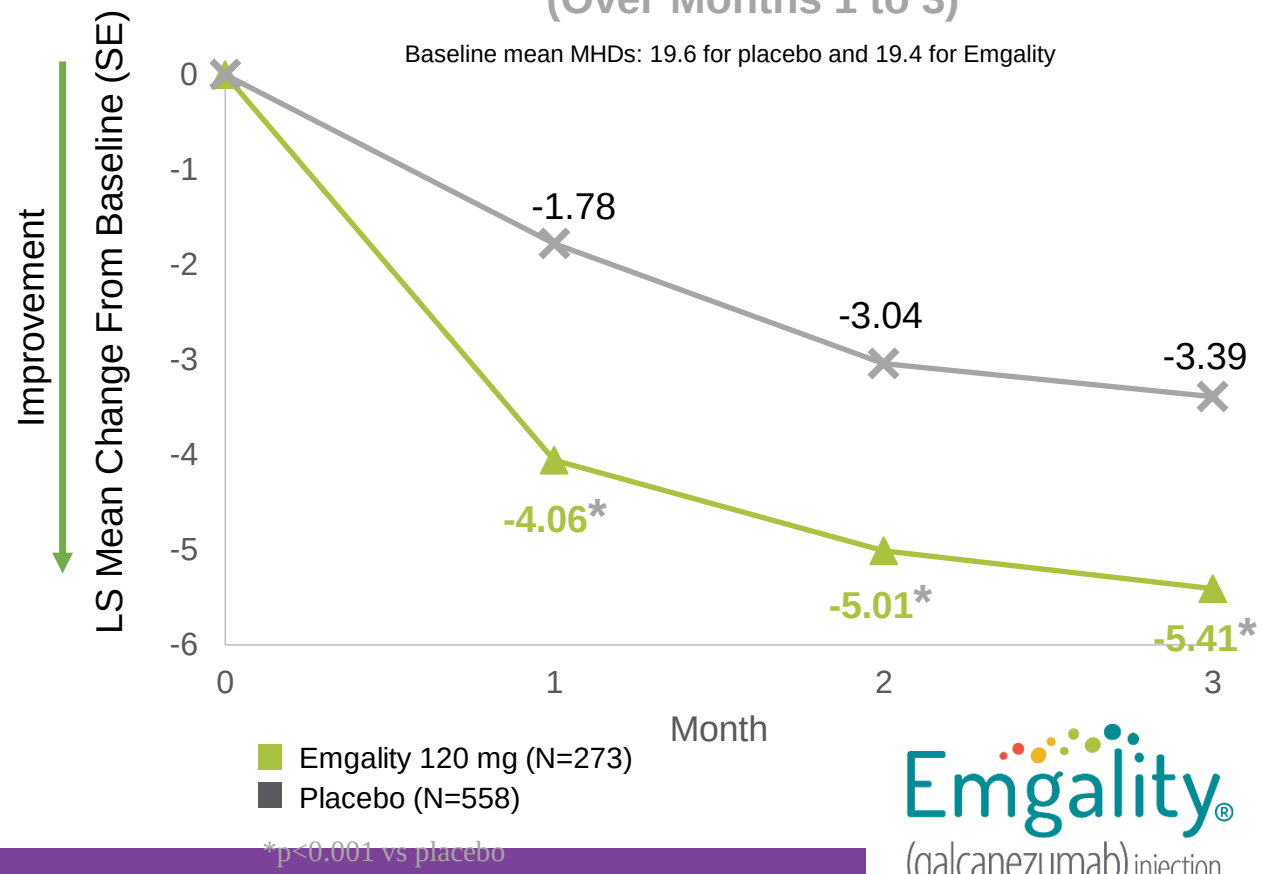
Emgality significantly reduced mean monthly MHDs as early as Month 1 and every following month (p<0.001)[1]

Mean Reduction of Monthly MHDs[1] (Over Months 1 to 3)

	Emgality 120 mg (N=273) Baseline: 19.4	Placebo (N=538) Baseline: 19.6
Mean change from baseline (days)	**-4.8***	**-2.7**

*p<0.001 vs placebo

Change From Baseline in Mean Monthly MHDs[1] (Over Months 1 to 3)



*p<0.001 vs placebo

Emgality® (galcanezumab) injection

1. Detke HC, et al. *Neurology*. 2018;91(24):e2211-e2221

5. Botox for CM健保規範

Botox健保規範

7.慢性偏頭痛之預防性治療(109/2/1)

(1)需經事前審查核准後使用。

(2)限神經內科或神經外科專科醫師診斷及注射。

(3)需符合慢性偏頭痛診斷：至少有3個月時間，每個月≧15天，每次持續4小時以上，且其中符合偏頭痛診斷的發作每個月≧8天。(重要限制：Botox對每個月頭痛天數≤14天的陣發性偏頭痛之安全性及有效性，尚無證據證實其療效)。

Botox健保規範

(4)患者需經3種(含)以上偏頭痛預防用藥物(依據台灣頭痛學會發表之慢性偏頭痛預防性藥物治療準則之建議用藥，至少包括topiramate)治療無顯著療效，或無法忍受其副作用

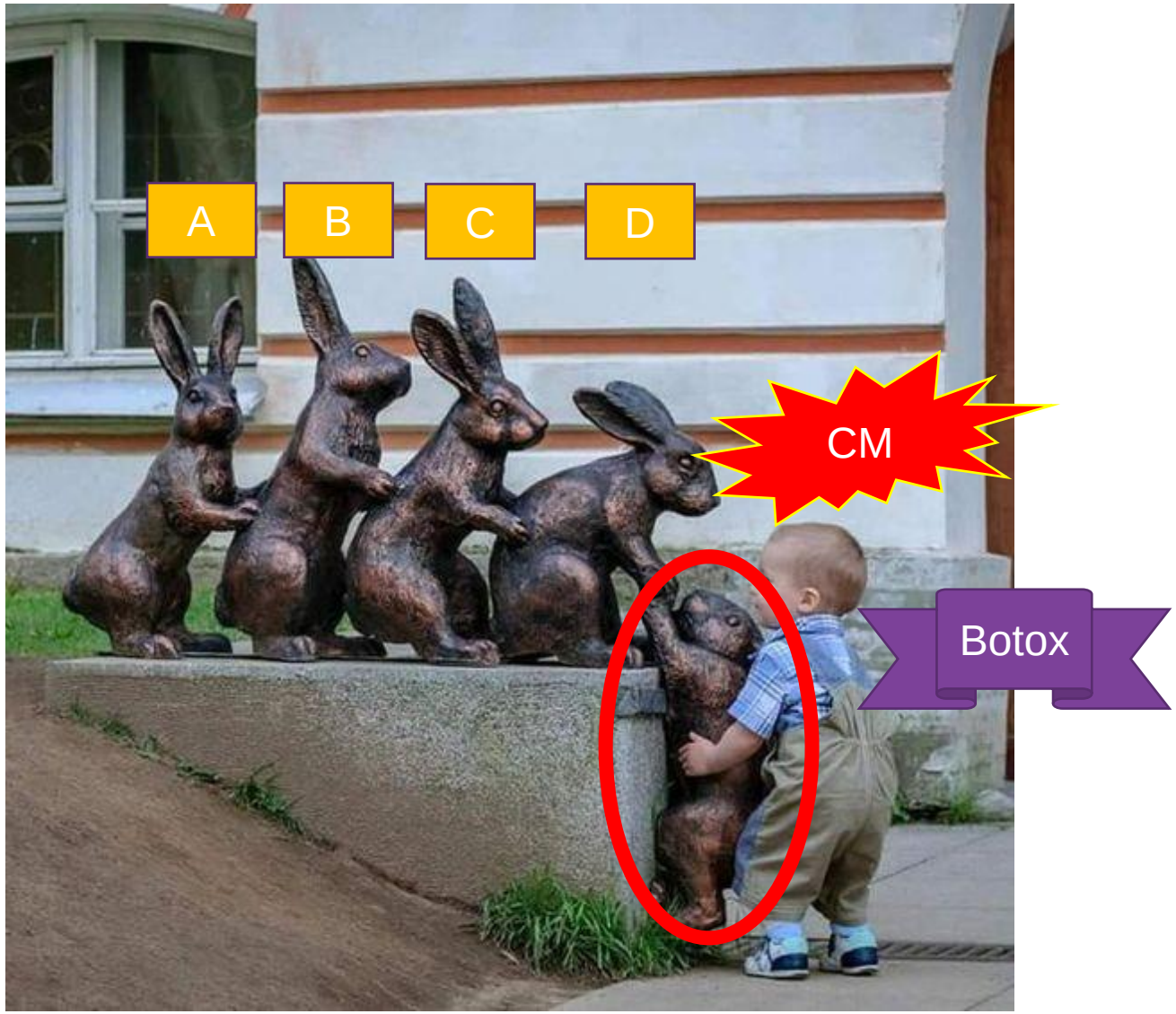
(5)每次注射最高劑量Botox 155單位，且每年最多4個療程。

(6)首次申請給付2個療程，2個療程治療之後，評估每月頭痛天數，需比治療前降低50%以上，方可持續給付。

(7)接續得申請一年療程，分為4次注射治療。療程完畢後半年內不得再次申請。

(8)若病況再度符合慢性偏頭痛診斷，得再次申請一年使用量時，需於病歷記錄治療後相關臨床資料，包括頭痛天數。

(9)神經內科、神經外科專科醫師需經台灣神經學學會訓練課程認證慢性偏頭痛診斷與Botox PREEMPT 155U 標準注射法。


A
B
C
D
CM
Botox

Medication Overuse Headache

PingKun Chen, MD PhD

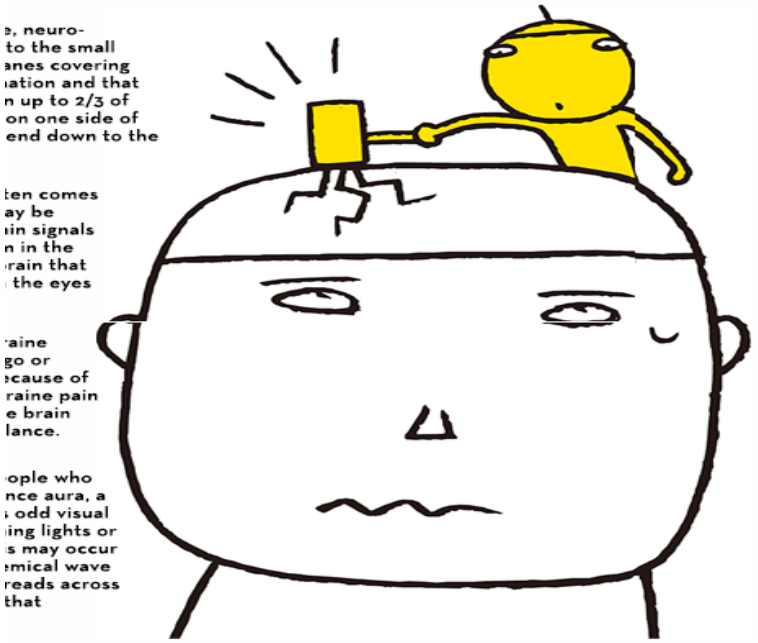
Bozhi Clinic, Taichung

Department of Neurology, China Medical University, Taichung

The international classification of headache disorders, 3rd edition (ICHD-3)

- **Headache classification committee of the international headache society (IHS)**
- 國際頭痛疾病分類第 3 版中文版

Episodic migraine (EM)	Chronic migraine (CM)
<15 headache days per month	**≥ 15 headache days** per month for ≥3 months
	≥ 8 migraine days per month for ≥3 months



ICHD-3. Cephalalgia 2018; 38 (1): 1-211

Medication-overuse headache (MOH)

Diagnostic criteria :

A. Headache occurring on ≥15 days/month in a patient with a **pre-existing headache disorder**

B. Regular overuse for >3 months of **one or more drugs** that can be taken for acute and/or symptomatic treatment of headache

C. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3. Cephalalgia 2018; 38 (1): 1-211

Medication-overuse headache

≥15 days and >3 months

8.2.3 Non-opioid analgesic (Paracetamol, NSAID, Aspirin)

≥10 days and >3 months

8.2.1 Ergotamine (麥角胺) , 8.2.2 Triptan (翠普登) ,
8.2.5 Combination-analgesic

≥10 days and >3 months

8.2.4 Opioid, 8.2.6 multiple drug

ICHD-3. Cephalalgia 2018; 38 (1): 1-211

ICHD-3 8.2 Medication Overuse Headache

- Headache occurring on ≥ 15days/m **with a pre-existing headache disorder**
- Regular overuse for >3 months
  - Ergotamine, triptans, opioids, combination-analgesics
    ≥10 days/m
  - Paracetamol, NSAID
    ≥15 days/m
- Not better accounted for by another ICHD-3 diagnosis

The International Classification of Headache Disorders, 3rd edition, Cephalalgia, 38 (2018)

Medication-overuse headache (MOH)

- MOH affects approximately 60 million people worldwide.
- MOH is the 3rd most common headache disorder.

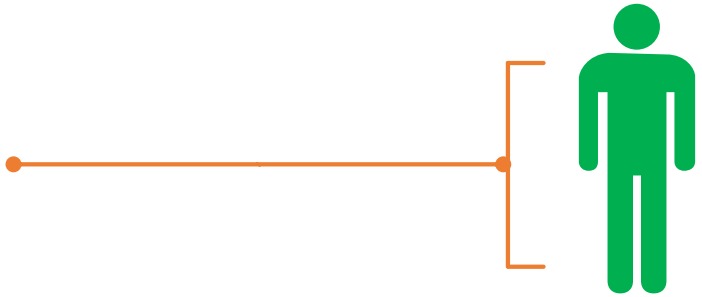
Vos T, et al. Lancet 2015; 386: 743–800.

Coding of MOH in ICHD-3

- Co-coding is suggested
  - ex. Chronic migraine and MOH
- No reversibility after withdrawal in necessary for MOH
- MO vs. MOH:
  - MO as adjective rather than etiology?

Prevalence of MOH

0.5-2.6% worldwide



Most recent data from Denmark, 2%, direct interview

Elderly (>65) 1.0% in Taiwan, 1.7% in IT; adolescents 0.3-0.5%

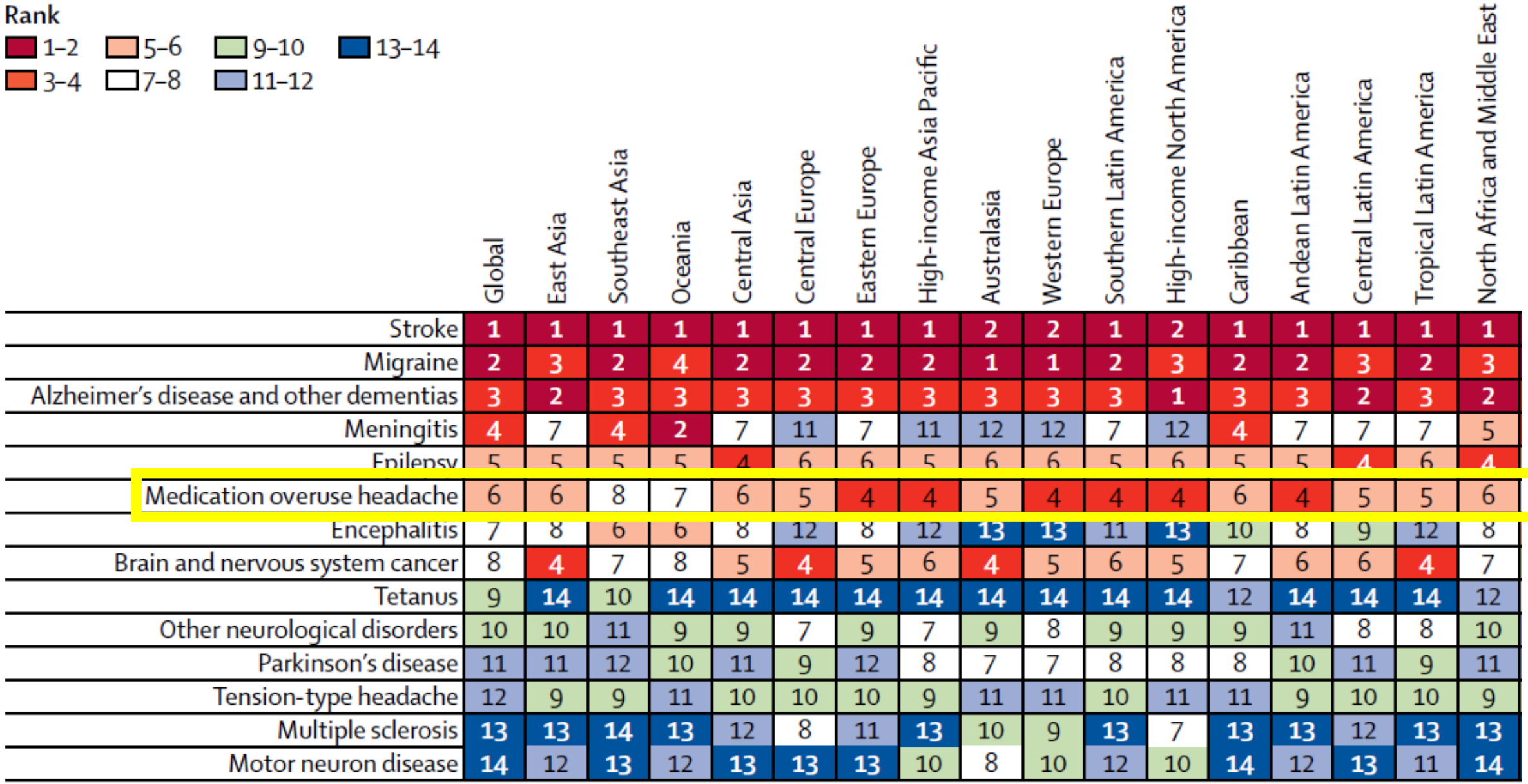
Westergaard ML et al, Cephalalgia. 2019 Sep 15:333102419876909.
Loder EW, Scher AI. Cephalalgia. 2019 Sep 15:333102419876907

Table 2 Selected population-based studies examining the proportion of individuals with chronic daily headache (≥15 headache d/mo) who are overusing medication

Study	Age range, y	Proportion overusing medication[a]
Castillo et al.[23]	14 and older	28
Dyb et al.[24]	13-18	36
Katsarava et al.[25]	16 and older	11
Lu et al.[26]	15 and older	34
Lundqvist et al.[27]	30-44	46
Prencipe et al.[28]	65 and older	38
Scher et al.[29]	18-65	23
Wang et al.[30]	65 and older	25
Wang et al.[31]	12-14	20
Wiendels et al.[32]	25-55	63
Zwart et al.[33]	20 and older	45

[a] Based on various definitions. Some figures have been estimated from the indicated publication.

Neurology 2017;89:1296–1304



	Global	East Asia	Southeast Asia	Oceania	Central Asia	Central Europe	Eastern Europe	High-income Asia Pacific	Australasia	Western Europe	Southern Latin America	High-income North America	Caribbean	Andean Latin America	Central Latin America	Tropical Latin America	North Africa and Middle East
Stroke	1	1	1	1	1	1	1	1	2	2	1	2	1	1	1	1	1
Migraine	2	3	2	4	2	2	2	2	1	1	2	3	2	2	3	2	3
Alzheimer's disease and other dementias	3	2	3	3	3	3	3	3	3	3	3	1	3	3	2	3	2
Meningitis	4	7	4	2	7	11	7	11	12	12	7	12	4	7	7	7	5
Epilepsy	5	5	5	5	4	6	6	5	6	6	5	6	5	5	4	6	4
Medication overuse headache	6	6	8	7	6	5	4	4	5	4	4	4	6	4	5	5	6
Encephalitis	7	8	6	6	8	12	8	12	13	13	11	13	10	8	9	12	8
Brain and nervous system cancer	8	4	7	8	5	4	5	6	4	5	6	5	7	6	6	4	7
Tetanus	9	14	10	14	14	14	14	14	14	14	14	14	12	14	14	14	12
Other neurological disorders	10	10	11	9	9	7	9	7	9	8	9	9	9	11	8	8	10
Parkinson's disease	11	11	12	10	11	9	12	8	7	7	8	8	8	10	11	9	11
Tension-type headache	12	9	9	11	10	10	10	9	11	11	10	11	11	9	10	10	9
Multiple sclerosis	13	13	14	13	12	8	11	13	10	9	13	7	13	13	12	13	13
Motor neuron disease	14	12	13	12	13	13	13	10	8	10	12	10	14	12	13	11	14

***Figure 4*: Ranking of age-standardised DALY rates for all neurological disorders by GBD region in 2015**
Data are for both sexes. DALYs=disability-adjusted life-years.

Lancet Neurol 2017; 16: 877–97

Is it true?

MOH is very Europe!!

Source of most recent 100citations of Pubmed for MOH and migraine

Line 1: Title contains ‘‘medication overuse’’ AND (headache or migraine);
Line 2: Title contains any of: Migraine, migraines, migraineur, migraineurs, excluding medication overuse publications; geographic location based on affiliation of first author;
Pubmed search 17 July 2019.

Loder EW, Scher AI. Cephalalgia. 2019 Sep 15:333102419876907

Supportive Evidence

Longitudinal data from Taiwan

- Analgesic overuse predicted persistent chronic daily headache after 2 years in a longitudinal, population-based study in Taiwan

Strong evidence of MOH in opioids and barbiturates

- The overuse of opioids and barbiturates is associated with migraine progression in both longitudinal population-based and clinic-based studies

Triptans and NSAID increased MOH in some group

- Triptans and nonsteroidal anti-inflammatory agents increased the risk of MOH in patients who experienced headaches for 10 days a month at baseline in the AMPP study

Different risk factors noted for CDH and MOH in HUNT studies

Wang SJ, et al. Neurology. 2000;54:314–9 Bigal ME, et al Headache. 2008;48(8):1157–68. Bigal ME, et al Neurology. 2008;71(22):1821–8 Paemeleire K, et al Neurology. 2006;67(1):109–13. Hagen K, et al Pain. 2012;153(1):56–61.

Challenge

Evidence of cause and effect is weak

- Never assign patient with episodic headache to overuse medication and compare the progression with who not overuse
- Observational studies that show an association between frequency or type of medication used and worsening headache could be result of other comorbidities or risk factors

Medication withdrawal does not help most patients with frequent headaches

- Withdrawal studies usually with high drop out rate and absence of control

AMPP study seems not support MOH

- American Migraine Prevalence and Prevention (AMPP) study, the frequency of symptomatic MO was not associated with chronic migraine incidence after controlling for headache frequency

Scher AI et al Neurology. 2017;89(12):1296-1304.

Risk Factors

Main Risk Factors for MOH

Risk factor	OR (95% CI)
Demographic	
Age (<50 years)	1.8 (1.3–2.4)
Female gender	1.9 (1.4–2.6)
Low educational level	1.9 (1.2–3.0)
Self-reported complaints	
Chronic musculoskeletal complaints	1.9 (1.4–2.7)
Gastrointestinal complaints	1.6 (1.1–2.2)
Anxiety or depression (HADS score ≥11)	4.7 (2.4–9.0)
Lifestyle	
Smoking	1.8 (1.2–2.5)
Physical inactivity	2.7 (1.2–6.3)
Metabolic syndrome	5.3 (1.6–24.6)
High daily caffeine intake (>540 mg versus ≤240 mg)	1.4 (0.8–2.5)
Medication	
Tranquillizers	5.2 (3.0–9.0)
Aspirin	0.5 (0.3–0.9)
Ibuprofen	0.7 (0.5–1.0)
Opioids	2.3 (1.3–3.9)

Nat Rev Neurol. 2016; 12: 575-83.

How long does it take?

Drug	Patients, n (%)	MCDO, y (SD)	MCMIF, single doses (SD)	MCMD, mg
Analgesics	46 (48)	4.8 (4.9)	113.9 (63.5)	
Analgesics	9 (9)	5.2 (5.0)	74.4 (47.5)	37,000
Analgesics + caffeine	25 (26)	5.4 (5.1)	135.1 (57.9)	48,774
Analgesics + codeine	4 (4)	5.5 (7.0)	129.0 (101.0)	72,550
Metamizol	2 (2)	2.3 (1.9)	34.5 (14.8)	17,250
Opioids	6 (7)	2.2 (2.1)	107.5 (52.3)	7,062
Triptans	38 (40)	1.7 (3.3)	18.6 (7.6)	
Sumatriptan	12 (13)	2.4 (3.1)	20.1 (8.3)	1,612
Zolmitriptan	20 (21)	1.7 (3.8)	18.4 (7.5)	46
Naratriptan	5 (5)	0.7 (1.3)	16.5 (7.8)	59
Rizatriptan	1 (1)	0.3 (—)	15.0 (—)	150
Ergots	12 (12)	2.7 (2.0)	36.7 (18.1)	53

Neurology 2002; 59: 1011-4.

Treatment
First step :
Education

Education works!!

A brief intervention of patient education

Usual care

lower headache frequency
16·5–24·6 vs 22·7–25·3 headache days/month
fewer medication days
10·7–21·9 vs 21·1–23·9 medication days/month

Kristoffersen ES, et al J Neurol 2016; 263: 344–53.

Education works!!

Italy: A 15-min education session that included advice to discontinue the overused medications was added to the standard treatment

79% reverting to a non-medication overuse

69% >=50% reduction in headache frequency at 2 m

Rossi P, et al. Eur J Neurol 2011; 18: 396–401.

Education works!!

Canada: a 90-min in-person didactic education session for 152 patients **awaiting their initial appointment** within the Center for Headache at the University of Toronto

MOH

53% → **39%**

Lagman-Bartolome AM, et al Headache 2018; 58: 109–17.

Nonpharmacologic Treatments: BIMOH study

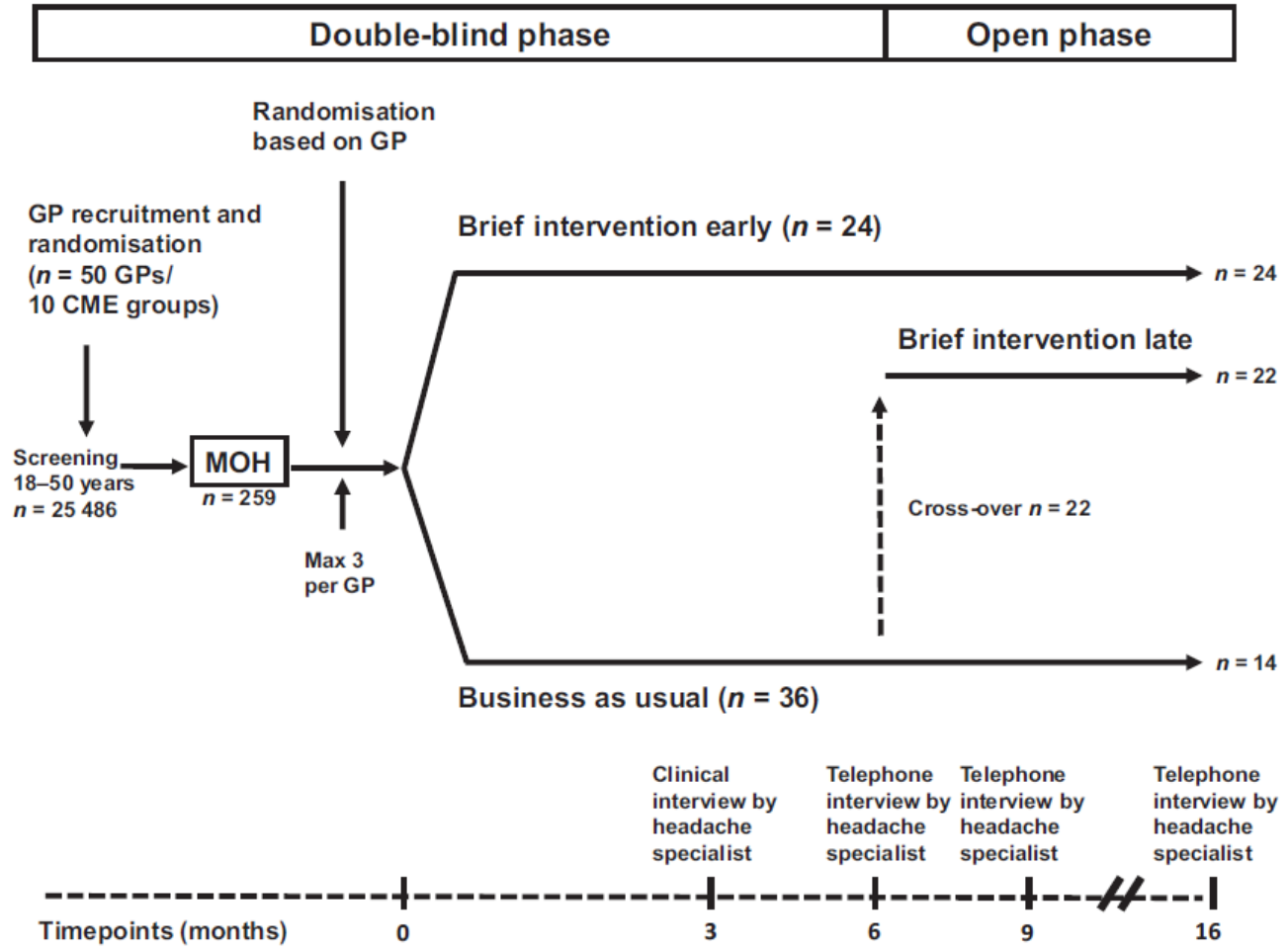
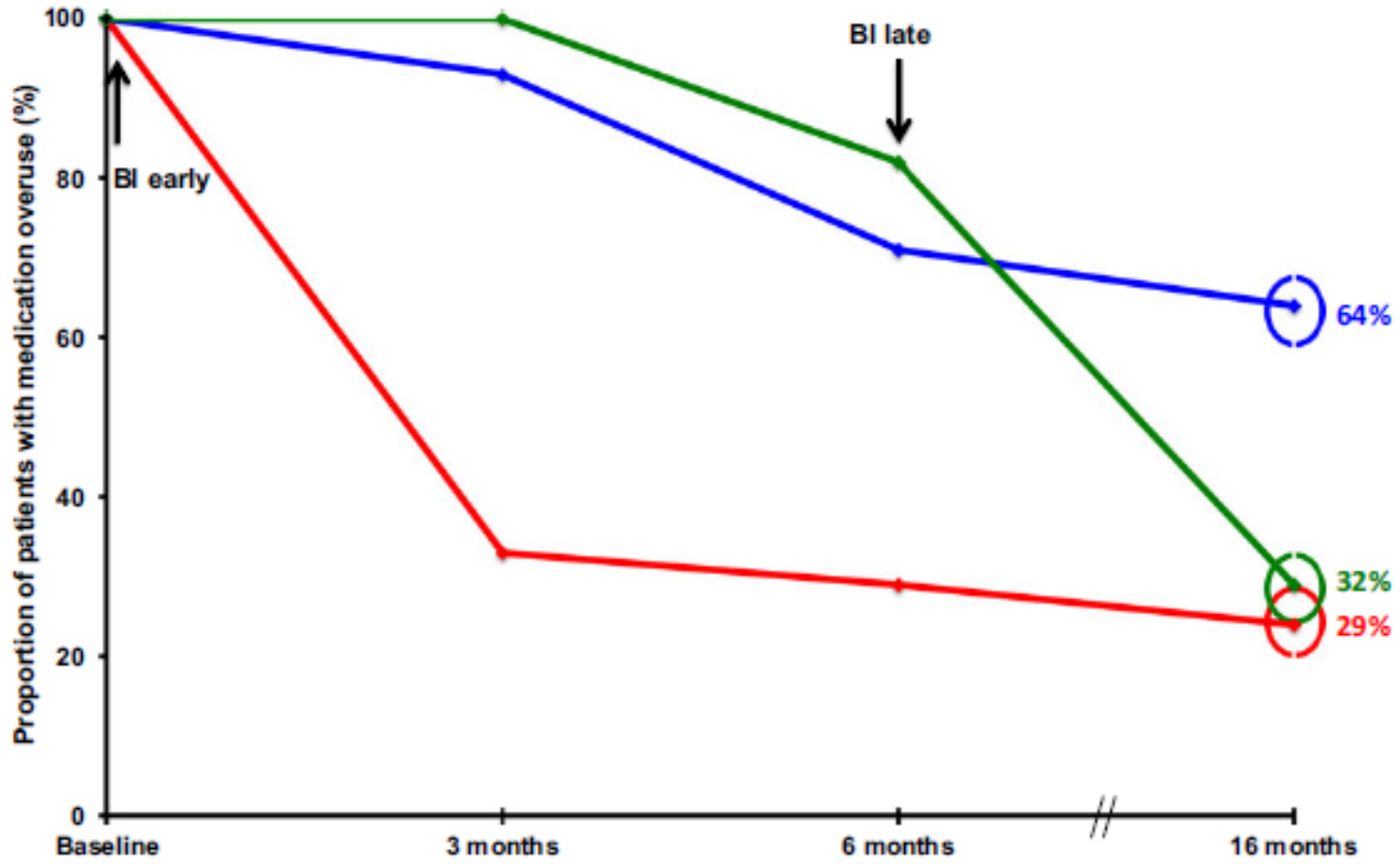


Figure 1 The flowchart illustrates the main time line as well as the timing of various moments for the patients. GP, general practitioner; CME, continuous medical education; MOH, medication-overuse headache.

Kristoffersen ES, et al Eur J Neurol 2017;24:883-891.

BIMOH study



Kristoffersen ES, et al Eur J Neurol 2017;24:883-891.

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Complete detoxification is the most effective treatment of medication overuse headache: A randomized controlled open-label trial

Program A

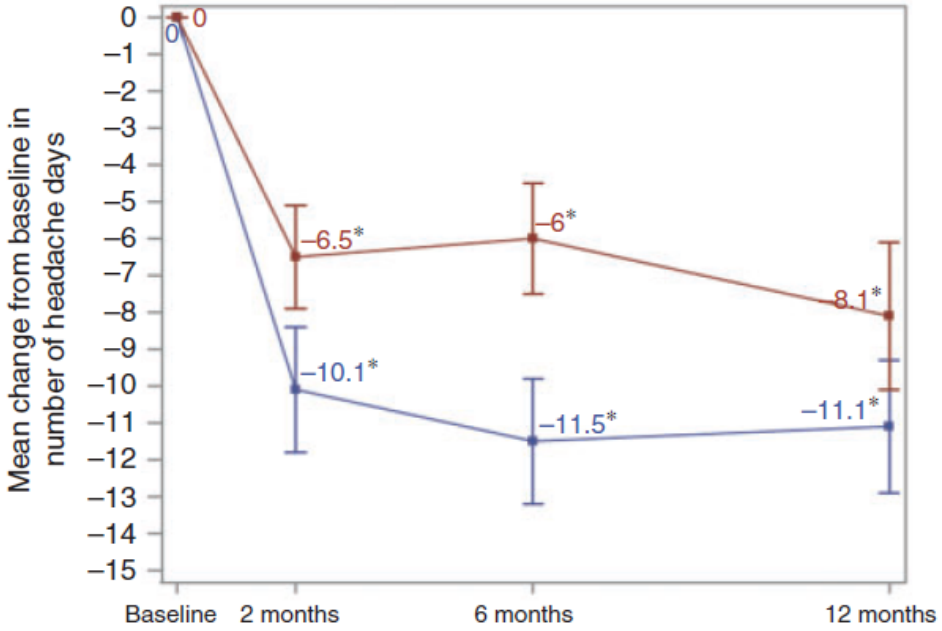
no analgesics or acute migraine-medication

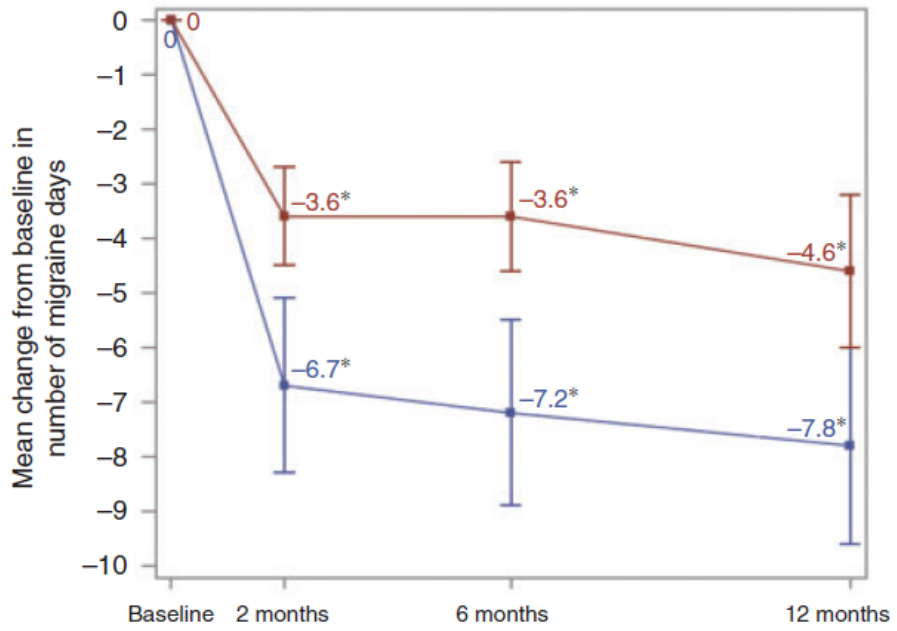
Program B

acute medication restricted to 2 days/week

Carlsen LN, et al. Cephalalgia, 2018; 38: 225–236.

Complete detox better than allowing PKs 2/wk

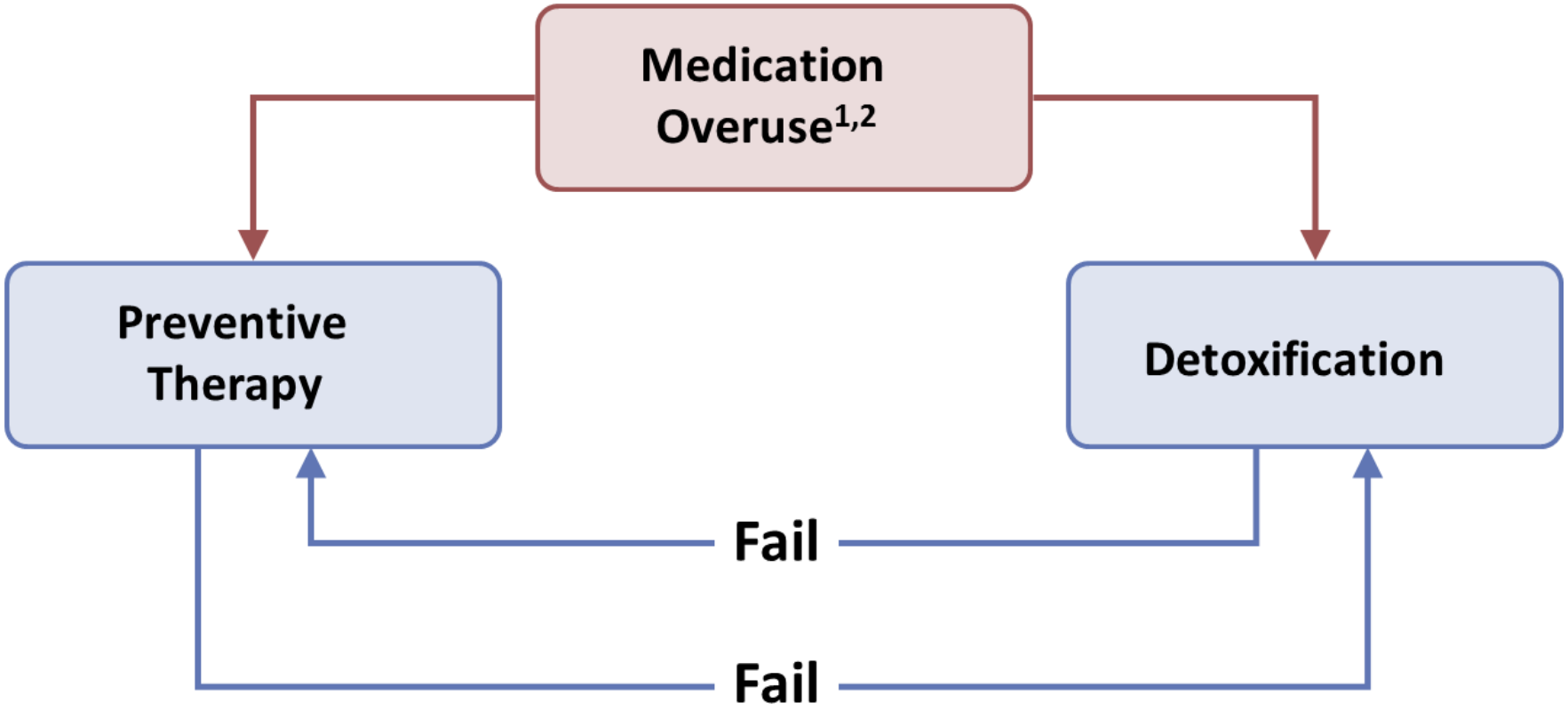




- Randomized controlled open-label trial
- 72 MOH outpatients
- Program A (complete detox) vs Program B (PK ≤2/wk)
- Preventives as indicated

Cephalalgia 2018; 38: 225–236.

Treatment of Medication Overuse



*≥15 days/month: simple analgesics, combinations of drugs; or ≥10 days/month: combination analgesics, ergotamines, triptans, opioids, barbiturates.

1. Diener HC, Limmroth V. *Lancet Neurol.* 2004;3:475-483.
2. Katsarava Z et al. *Curr Neurol Neurosci Rep.* 2009, 9:115-119.

Preventive medications for chronic migraine

A

Antiepileptics

- Topiramate
- Valproate
- Gabapentin

B

β-blockers

- Propranolol
- Atenolol
- Metoprolol

BoNTA

C

Ca^{2+} channel blockers

- Flunarizine
- Verapamil

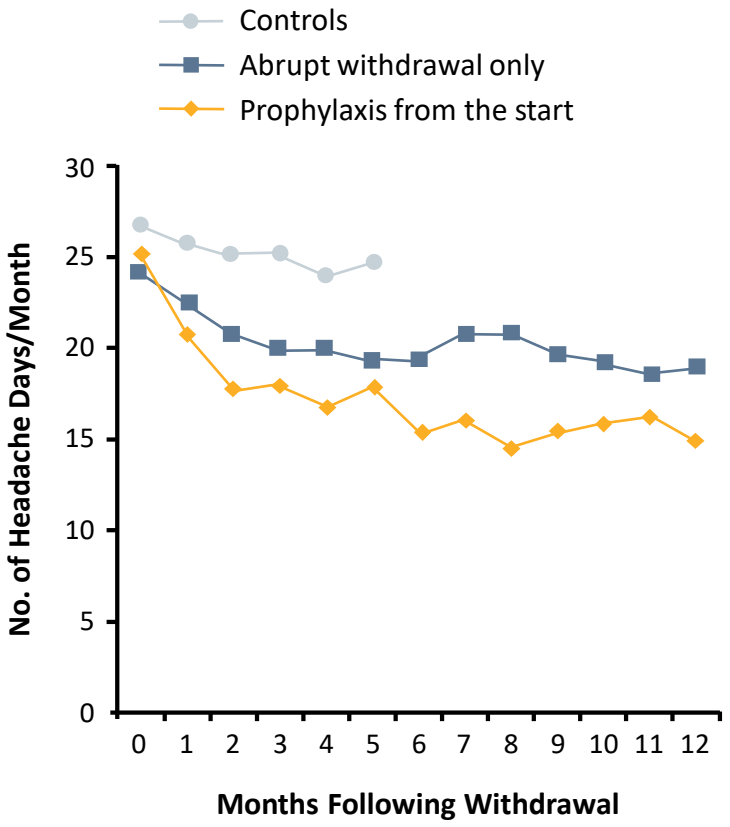
D

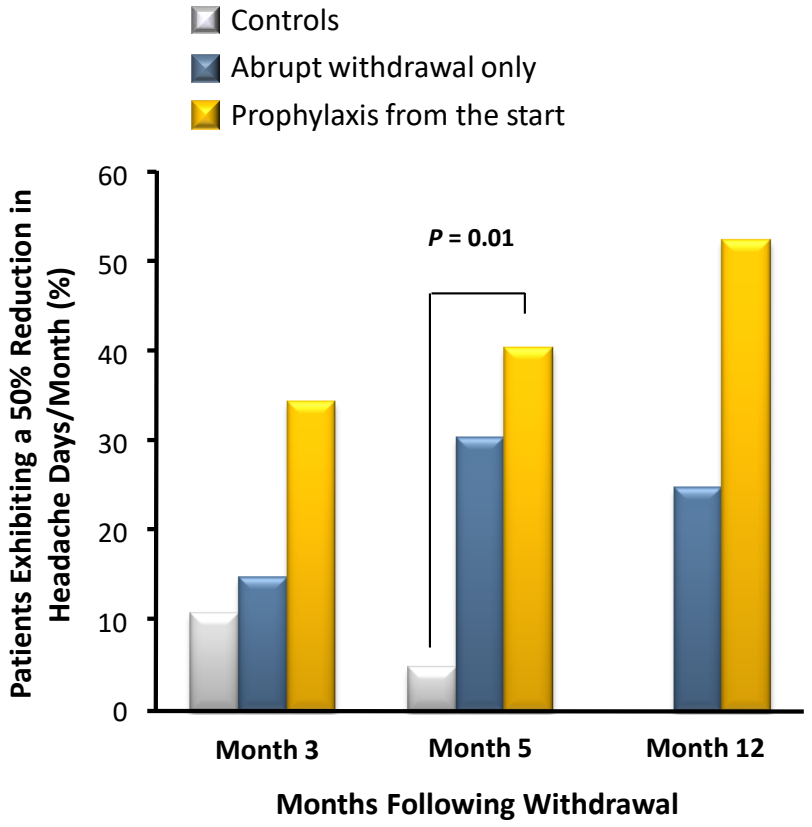
antidepressants

- Amitriptyline
- Nortriptyline
- Venlafaxine

DB-PC Trials in chronic migraine: BoNTA, Topiramate

Long-Term Outcomes: Preventive Treatment vs. Abrupt Withdrawal of Acute Medications

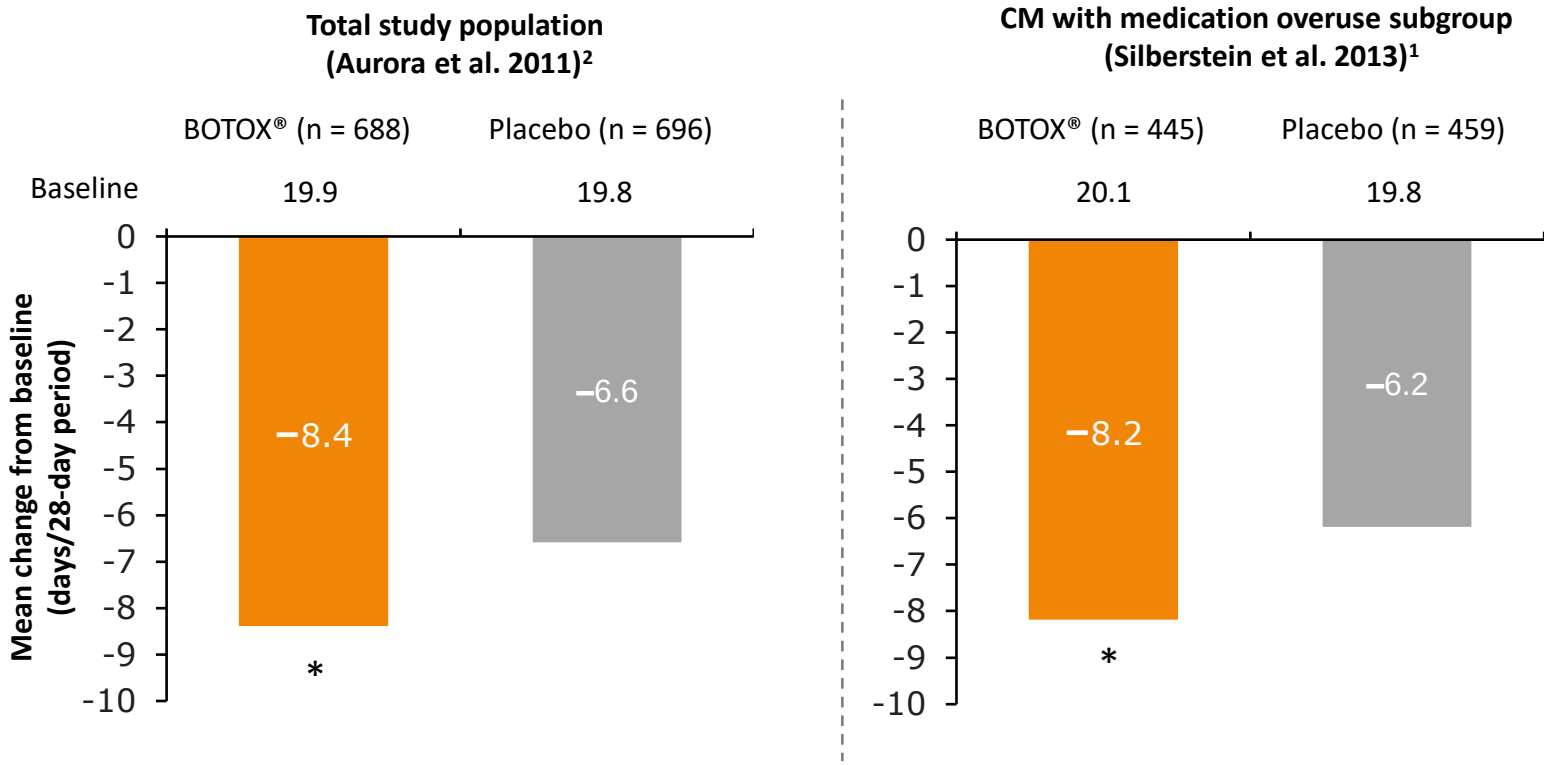




Hagen K et al. *Cephalalgia.* 2009;29:221-232.

PREEMPT primary endpoint in CM with medication overuse subgroup: frequency of headache days

In patients with CM with MOH, BOTOX® significantly improved frequency of headache days vs placebo (BOTOX® –8.2; placebo –6.2; $p < 0.001$)[1]



*$p < 0.001$ vs placebo.

1. Silberstein et al. J Neurol Sci 2013;331:48–56. 2. Aurora et al. Headache 2011;51:1358–73.

Topiramate

Table 1 Key differences between US and European Union trial patient populations

Parameter	US (18) n=306	European Union (19) n=59
Criteria used to diagnose chronic migraine	Silberstein/Lipton	ICHD-II
Other concomitant migraine preventive therapy	Not allowed	Allowed
Acute medication overuse (MO)	Permitted medication use no more than 4 days/week*	Patients overusing medication allowed to participate
MO during prospective baseline	37.6%	78%
Target dose of topiramate	100 mg/day	100 mg/day (dosing up to 200 mg/day)

*Some subjects could be classified as having medication overuse headache via the current International Classification of Headache Disorders, second edition (ICHD-II) definition.

Cephalalgia, 2009; 29: 1021–1027.

Triptan overusers had better response to TPM

Table 2 US trial: mean change in migraine/migrainous days as a function of type and frequency of medication overuse

	Change from baseline, mean days (S.D.)				
	Topiramate		Placebo		
Acute medications	*n*	Mean	*n*	Mean	*P*-value*
Triptans ≥ 10 days	28	−6.4 (5.24)	23	−3.7 (6.35)	0.037
Simple analgesics ≥ 15 days	33	−8.0 (6.43)	29	−6.6 (6.23)	0.326
Any combination ≥ 15 days	48	−8.0 (5.73)	50	−5.8 (5.43)	0.081
Any combination 15–18 days	21	−8.8 (3.47)	29	−5.9 (4.80)	0.084
Any combination > 18 days	27	−7.5 (7.01)	21	−5.6 (6.32)	0.097
Change in use (between −5 to +10 days)	15	−3.4 (5.17)	23	−0.9 (3.53)	0.268
Change in use (between −5 and −25 days)	44	−9.2 (5.40)	33	−8.3 (4.41)	0.269

*Test for no difference between treatments from ANCOVA model with effects for treatment, centre and baseline as covariate. 'Any combination' refers to any combination of triptans, opioids and analgesics.

Cephalalgia, 2009; 29: 1021–1027.

Withdrawal Treatment: Necessary?

Relapse

- Approx. 25-35% of patients experience relapse.
- Predictors for favorable outcome: migraine, triptan overuse
- Predictors for poor outcome: TTH, opioid overuse, comorbid psychiatric disorders

Cephalalgia 2015; 36: 371–386.

Risk Factors of MOH Relapse

Higher relapse risk after detoxication

- higher depression scores
- a longer duration of chronic headache
- higher number of headache days per month
- tension type headache at the primary headache diagnosis
- carrier SLC6A4 variant

Lower relapse risk after detoxication

- migraine at the primary headache diagnosis
- rs4680G allele carriers
- the catechol-O-methyltransferase rs6269G-rs4680G haplotype

Bottiroli S, et al. Cephalalgia. 2019 ;39(1):135-147. Zidverc-Trajkovic JJ et al Cephalalgia. 2018;38(2):265–73.
Cargnin S, et alEur J Neurol. 2014;21(7):989–95.

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Psychological, clinical, and therapeutic predictors of the outcome of detoxification in a large clinical population of medication-overuse headache: A six-month follow-up of the COMOESTAS Project

Bottiroli et al. Cephalalgia, 2019 Jan; 39(1): 135–147

The COMOESTAS project

- COntinuous MOnitoring of Medication Overuse Headache in Europe and Latin America: development and STAndardization of an Alert and decision support System.

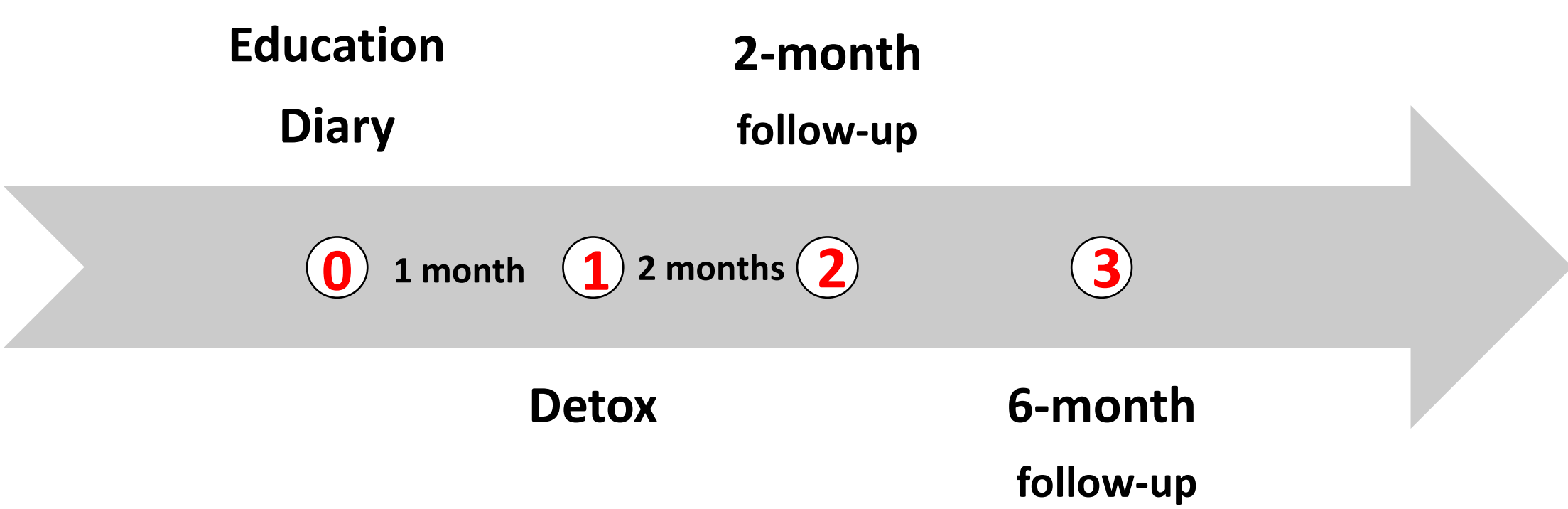
- To develop a detoxification program for global implementation.

- 4 European and 2 Latin American headache centers.

  - **Denmark, Germany, Italy, Spain, Argentina and Chile**

Jellestad PL, et al. Cephalalgia 2019; 39 (2): 274-285.

Procedures


Education
Diary
2-month
follow-up
0
1 month
1
2 months
2
3
Detox
6-month
follow-up

COMOESTAS project

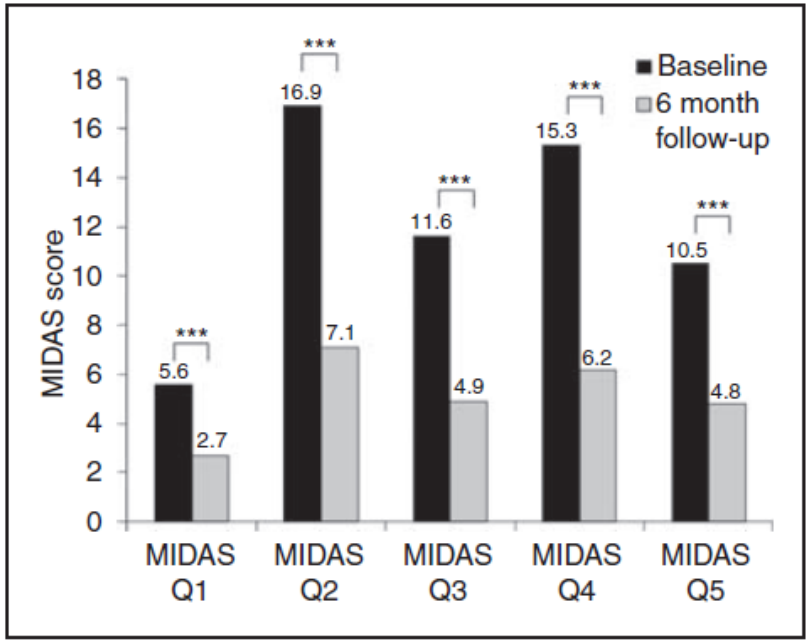
Prophylactic drugs+medication withdrawal
70.9% completed (492/694)

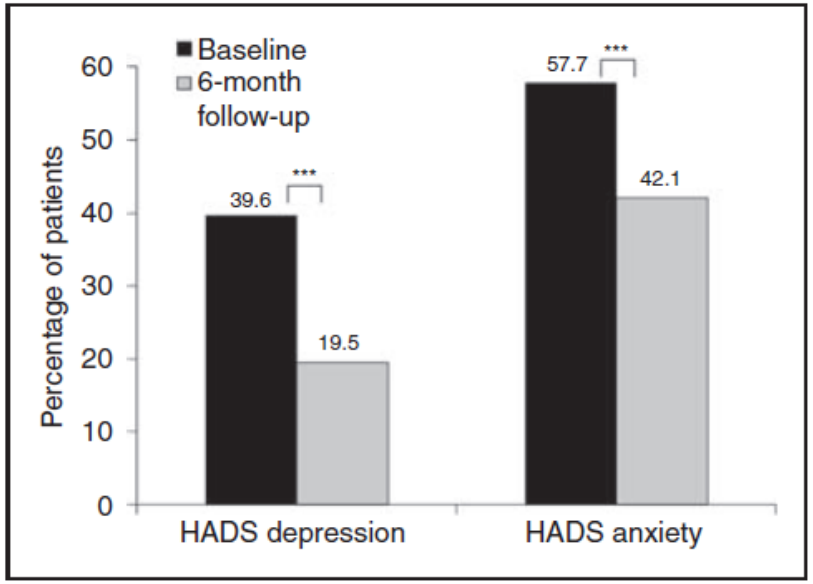
58% **Headache days reduction**
23.6 to 9.8 days/m at 6 m (p<0.001).
44% reduction in 1st month
further down to 60% at 6 months.

57% **MIDAS reduction**
59.9 to 25.7 (p<0.001).

51% **Number of patients with depression**
from 195 to 96 (p<0.001).

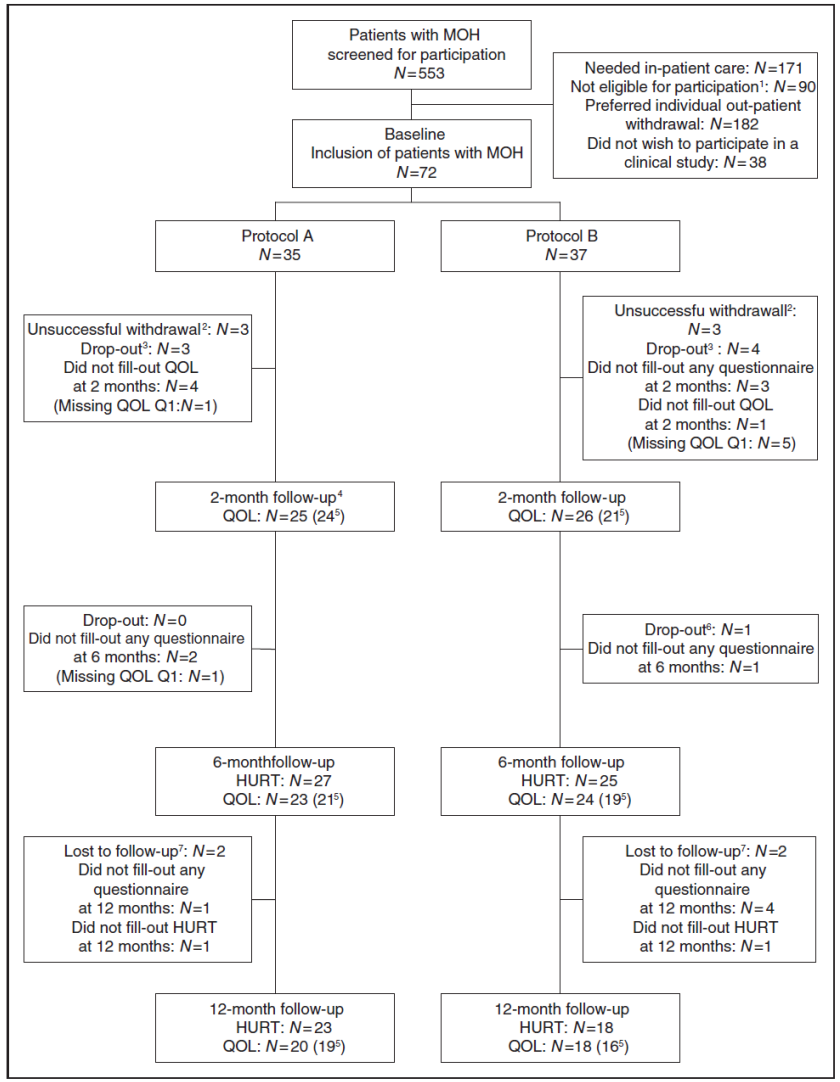
27% **Number of those with anxiety**
from 284 to 207 (p<0.001).





Bendtsen L et al. Cephalalgia 2014,34: 426–433

Complete withdrawal most effective to reduce disability in patients with MOH



A prospective, outpatient study

- Program A (No acute analgesics or migraine medications for 2 m)
- Program B (restricted to 2 days/week for 2 m)

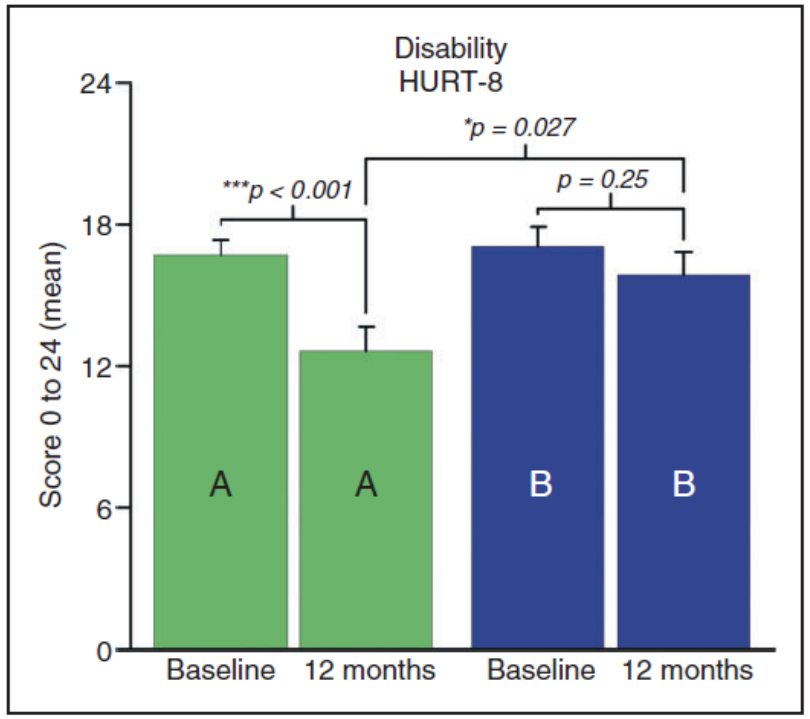
Follow-up evaluation

- disability and headache burden by the Headache Under-Response to Treatment index (HURT) at 6 and 12 months.
- Quality of life by EUROHIS-QOL 8-item at 2-, 6-, and 12-month follow-up

Primary endpoint

- disability change at 12 months.

Nielsen M et al. Cephalalgia. 2019 ;39:863-872



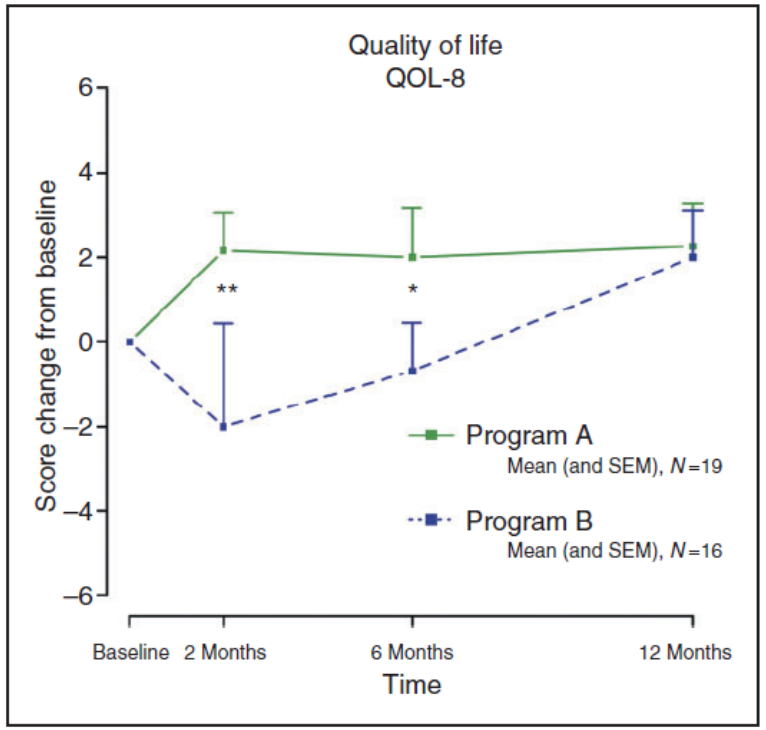


Table 3. HURT scores and QOL score.

		Completing questionnaire until 6 months			Completing questionnaire all 12 months		
		Baseline	6 months	*p*-values	Baseline	12 months	*p*-values
HURT-3[1]	Program A	6.7 (0.4)	5.2 (0.5)	**0.005**	6.5 (0.4)	4.3 (0.6)	< **0.001**
	Program B	7.3 (0.4)	6.6 (0.5)	0.086	7.1 (0.5)	6.8 (0.5)	0.68
HURT-8[1]	Program A	16.9 (0.6)	13.4 (0.9)	< **0.001**	16.7 (0.7)	12.6 (1.1)	< **0.001**
	Program B	17.4 (0.6)	16.0 (0.6)	0.072	17.1 (0.8)	15.9 (0.9)	0.25
QOL-8[2]	Program A	27.6 (1.1)	30.1 (1.3)	0.082	28.1 (1.1)	30.4 (1.0)	**0.037**
	Program B	23.9 (1.2)	23.0 (1.6)	0.37	23.7 (1.3)	25.7 (1.6)	0.096

Nielsen M et al. Cephalalgia. 2019 ;39:863-872

However, high drop out rate should be considered

Table 3 Proportion of patients with presumed medication overuse headache who improved with medication withdrawal as the sole treatment

Study, year/no. of patients	Follow-up duration, mo[a]	Proportion completing withdrawal[a]	Proportion of completers who improved	Proportion of all patients who improved[a]	Study definition of improvement
Studies identified in Chiang et al.[42] review					
Grande et al.,[43] 2011/n = 140	18	Unknown	42	33	<15 Headache d/mo
Hagen et al.,[44] 2009/n = 20	3	91		15 (Intention-to-treat)	≥50% Reduction in headache days and no medication overuse
Rossi et al.,[45] 2011/n = 100	2	79	87	69	≥50% Reduction in headache days
Zeeberg et al.,[46] 2006/n = 337	2	64	45	29	≥1% Reduction in headache days
Relevant studies published after Chiang et al.[42] review					
Sarchielli et al.,[47] 2014/n = 44	3	100	24	24 (Withdrawal + placebo group)	≥50% Reduction in headache days
Pijpers et al.,[48] 2016/n = 416	2-3	68	42	27	≥50% Reduction in headache days

[a] Calculated or estimated from original publication in some cases. See appendix e-1 notes for details of data extraction or calculation.

Scher AI et al Neurology. 2017;89(12):1296-1304.

Withdrawal maybe not necessary

- Both clinical trial of topiramate(topamax), onabotulinumtoxinA (botox) showed the reduction of headache days did no differ in chronic migraine patients with or without MOH

Diener HC et al. Lancet Neurol. 2019;18(9):891-902.

Proposed protocol for patients with MOH

Outpatient treatments

(a) Confirm the diagnoses of MOH.
(b) Record baseline data especially headache and analgesics use frequencies; a headache intake form and a headache diary are recommended.
(c) Give necessary education including oral advise to abruptly or gradually withdrawal the overused medications
(d) Prescribe preventive medications
(e) Decide the responses mainly according to headache and analgesics use frequencies; if failure, consider inpatient treatments

Lai TH, Wang SJ. Curr Pain Headache Rep (2016) 20: 5

Proposed protocol for patients with CDH and MOH

In patient treatments

(a) Replace all the overused medications with rescue therapy
(b) Monitor the response by pain score
    (i) If pain score is >3, adjust rescue therapy dosage (e.g., prochlorperazine from 5 mg to 10 mg) or consider an alternative (e.g., from prochlorperazine to valproate)
    (ii) Discharge may be considered if
        (A) Pain score is consistently <3 for more than 1 day or
        (B) The length of hospitalization exceeding 1 to 2 weeks

Lai TH, Wang SJ. Curr Pain Headache Rep (2016) 20: 5

Detoxification of overused abortive treatment during admission (IV)

- Dihydroergotamine
- **Prochlorperazine**
- **Magnesium sulfate**
- Ketorolac
- **Methylprednisolone**
- **Lidocaine**
- Valproic acid
- Olanzapine

Lu SR et al. Headache 2000;40: 724-729

Inpatient detox works better for complicated MOH

Table 3 Primary and secondary outcome measures

	Group A (n = 46)	*Group B (n = 46)*	*Group C (n = 45)*	*Statistics*
Patients missing follow-up visits n(%)	11 (23.9)	9 (19.5)	2 (4.4)	$p < 0.025$*
Responders n(%)	28 (60.8)	28 (60.8)	40 (88.9)	$p = 0.003$*
Responders with headache improvement n (%)	25 (54.3)	26 (56.5)	38 (84.4)	$p = 0.003$§
Percent reduction in number of headache days/month mean ± SD (median)	44 ± 25 (50)	49.8 ± 28 (52)	73 ± 22 (76)	$p < 0.001$¤
Percent reduction in the number of days with use of symptomatic medication mean ± SD (median)	62.5 ± 23 (64)	63.6 ± 26 (64)	75.2 ± 23 (78)	$p = 0.001$¤
Percent reduction in the number of symptomatic medication mean ± SD (median)	67.8 ± 18 (68)	69.7 ± 22 (70)	83.3 ± 20 (84)	$p = 0.001$

*Fisher's test, § Chi-square test, ¤ Kruskal-Wallis test.

J Headache Pain 2013, 14:10

IV prochlorperazine detox for MOH Taipei, Taiwan

- N=95
- Mean hospital stay 6.2 days
- 90% with 50% reduction of headache intensity
- Headache free (63%) at discharge (successfully detoxified)
- Follow up at 14.3 months (5-33 months)
  - 30% relapse to MOH

Lu SR et al. Headache 2000;40: 724-729

Proposed treatment path for patients with MOH

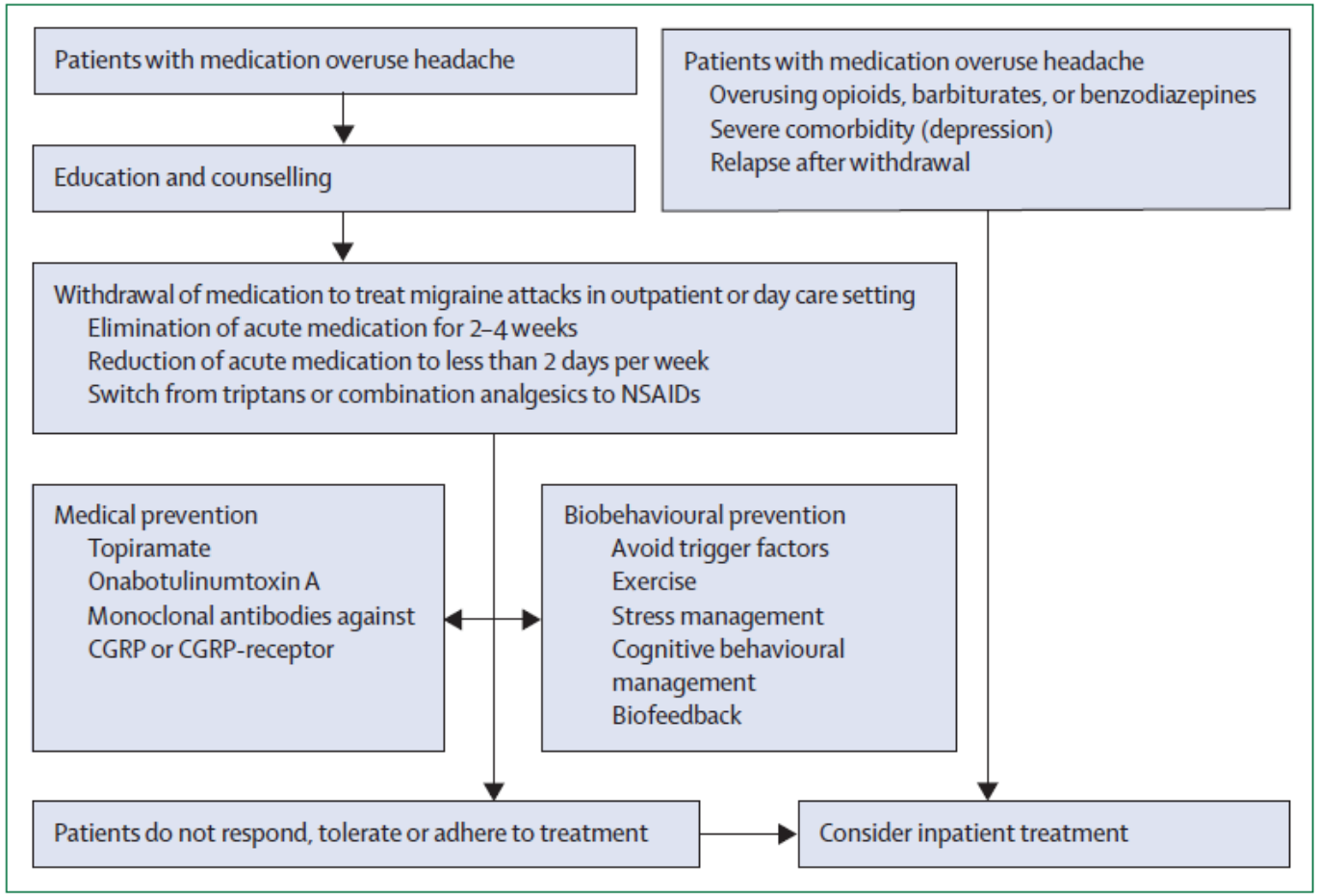


Figure 1: **Proposed treatment path for patients with medication overuse headache**
NSAID=non-steroidal anti-inflammatory drug. CGRP=calcitonin gene-related peptide.

Diener HC et al. Lancet Neurol. 2019;18(9):891-902.

Algorithm for treatment of CM with MOH

1. Patient education
2. Anticipation/ addictive behaviour
3. Start preventive treatment: topiramate/flunarizine followed by BOTOX®
4. Outpatient detoxification process with transitional treatments
   a. Oral DHE or prochloroperazine
   b. NSAIDs prn use
5. Hospitalization
   a. Major depression
   b. Outpatient failure

Thanks for your time.

Neuroimaging in the Diagnosis of Headache Disorders

楊 富 吉

Fu-Chi Yang, MD, PhD

Associate Professor, Department of Neurology,

Tri-Service General Hospital

Outline

- **Introduction**
  - Neuroimaging techniques
  - Warning signs
- **Neuroimaging in common secondary headaches**
  - Emergent conditions
  - Painful cranial neuropathies
- **Take home messages**

IHS Classification ICHD-III

Part I: The Primary Headaches

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders

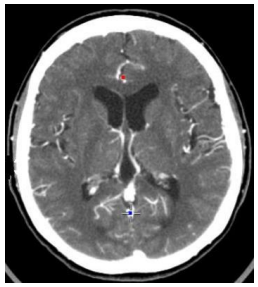
Part II: The Secondary Headaches

5. Headache attributed to trauma or injury to head and/or neck
6. Headache attributed to cranial or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structures
12. Headache attributed to psychiatric disorder

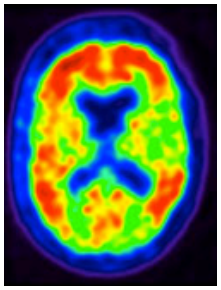
Part III: Cranial Neuralgias Central and Primary Facial Pain and Other Headaches

13. Painful cranial neuropathies and other facial pains
14. Other headache disorders

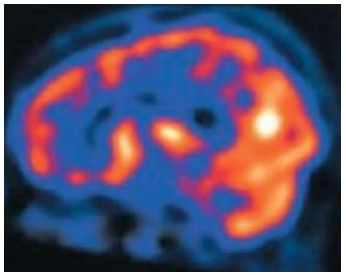
Neuroimaging techniques



CT

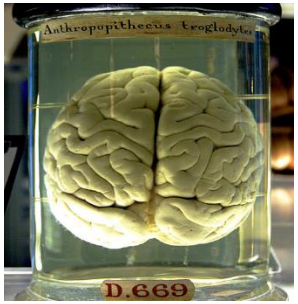


PET

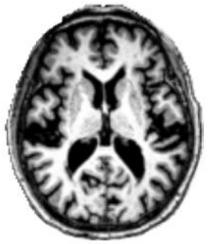


SPECT

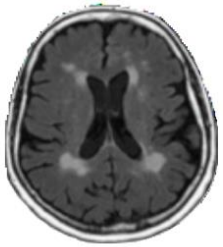
Structural



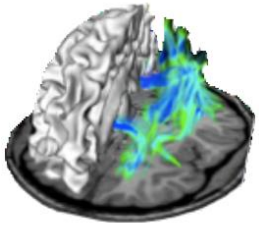
Functional



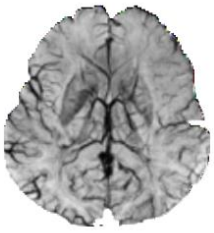
T1



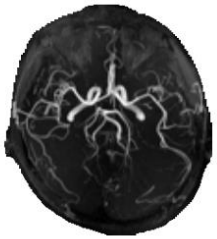
FLAIR-T2



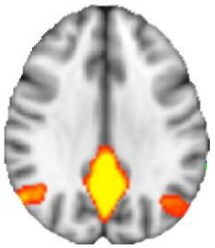
dMRI



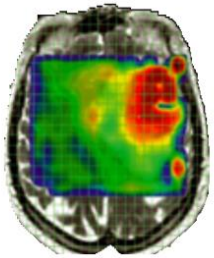
SWI



MRA



fMRI

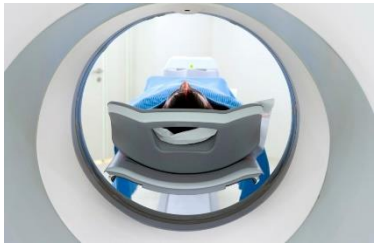


MRS

Structural MRI

Functional MRI

Chance of finding a lesion?



- **A large review of over 3026 scans:**
  - 0.8% brain tumors
  - 0.2% AV malformations
  - 0.3% hydrocephalus
  - 0.1% aneurysm
  - 0.2% subdural hematomas
  - 1.2% CVA

Evans et al, Neurol Clin.1996

- **A Chinese hospital study of 1070 controls and 1070 primary headaches :**
  - 4 (0.58%) patients with primary headache
    (hydrocephalus, tumors on the throat and nose)
  - 5 (0.73%) healthy controls
    (cerebral infarction, acoustic schwannoma, cavernous angioma)

Wang et al. Headache. 2018

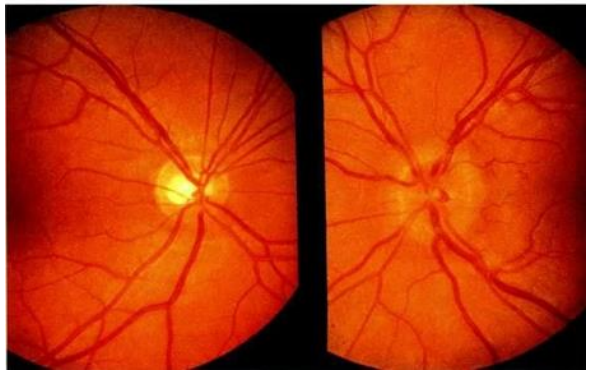
Red flags - "SNOOP10"

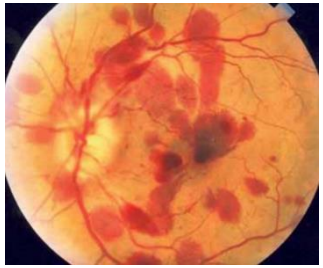
- **S**ystemic symptoms (fever, neoplasm, HIV/immunocompromised)
- **N**eurologic symptoms or signs (weakness, convulsion, diplopia, ataxia)
- **O**nset sudden (peak intensity within 1 minute, worst)
- **O**lder age (new onset after age **50**)
- **P**attern change (progressive, evolution to daily headache)
- **P**recipitated by Valsalva (i.e. coughing, exercise, sex)
- **P**ostural aggravation (i.e. increases when upright or lying down)
- **P**ost-traumatic onset , **P**regnancy (or puerperium), **P**ainkiller overuse
- **P**apilledema, **P**ainful eye with autonomic features

Do et al. Neurology 2019; Young et al. Cephalalgia 2018

Neurologic Examination

- Vitals (particularly BP), consciousness
- Pupil symmetry, reactivity and fundoscopy
- Visual fields
- Eye movements (CN3, 4, 6)
- Motor – look for asymmetrical weakness
- Reflexes – look for asymmetry (increased reflexes)
- Signs of meningeal irritation (Kernig's and Brudzinski's signs)
- Coordination and gait



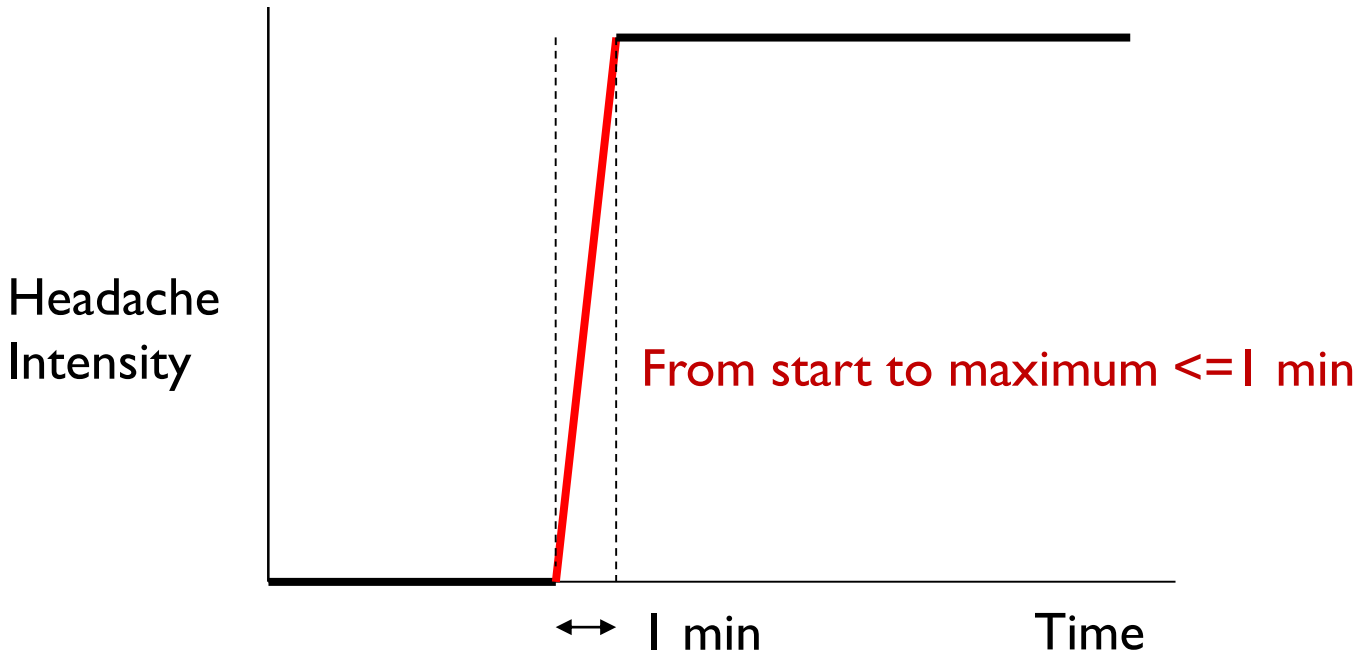


Barritt et al. The Practitioner. 2016

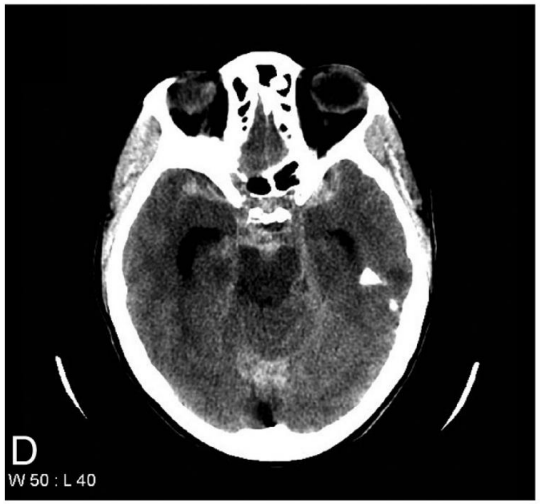
Entezari st al. Eur J Ophthalmol. 2009

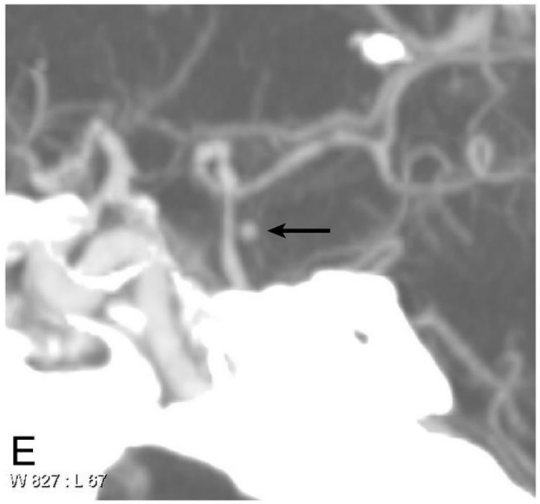
Neuroimaging in the emergency

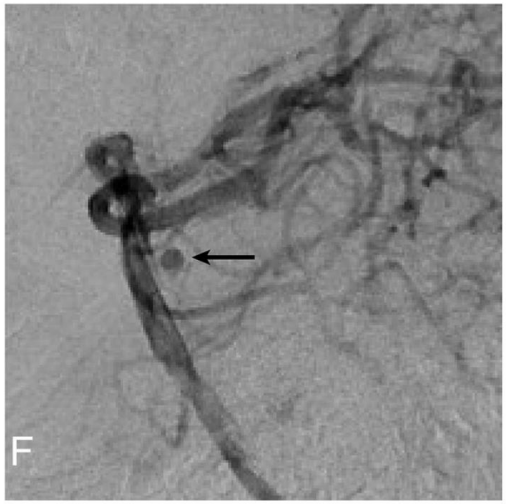
(thunderclap headaches)

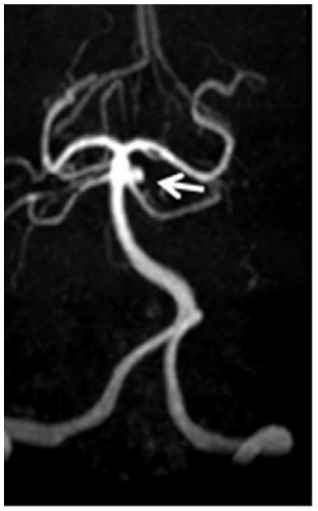


Subarachnoid hemorrhage (SAH) - I





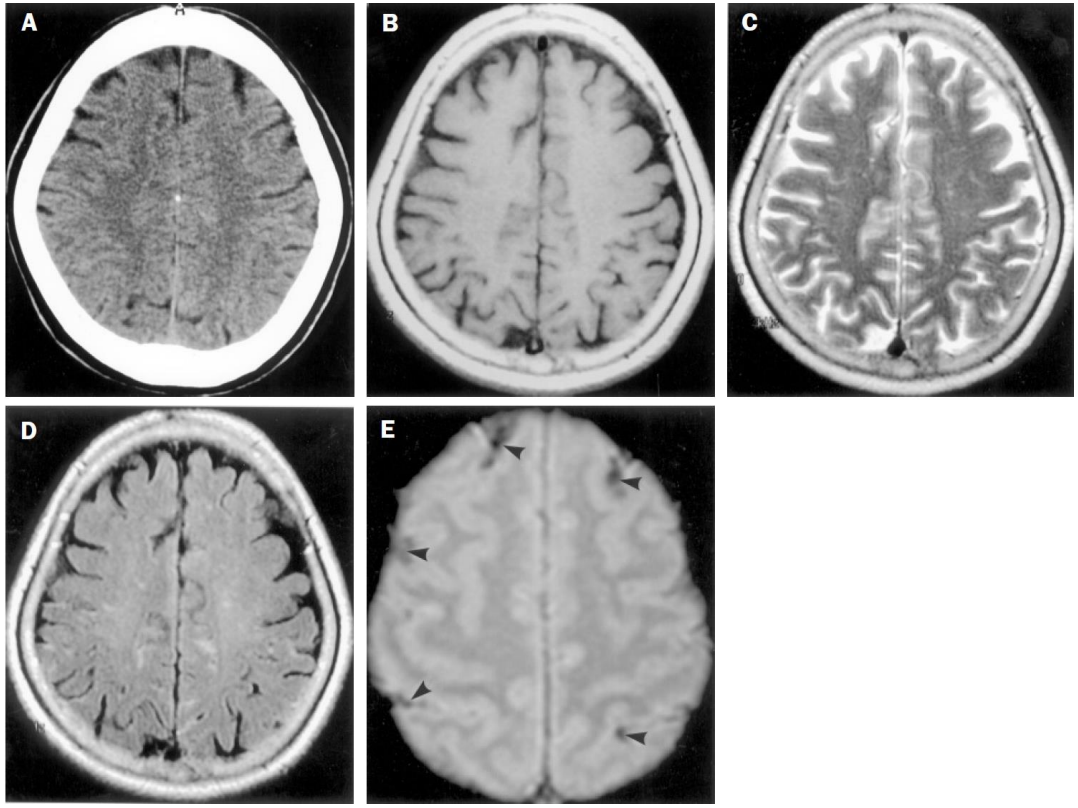




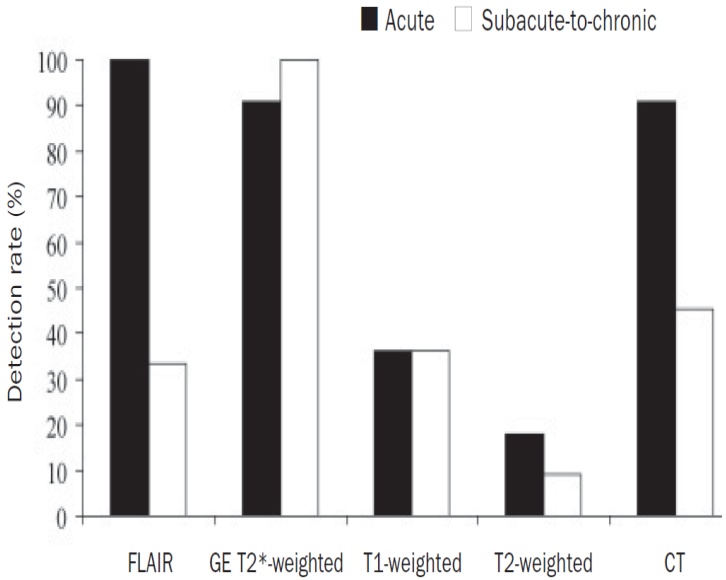
- Acute stage: CT scan without contrast (lower cost and faster time)
- Sensitivity: 98% in 12 hours; 93% in 24 hours; 50% in 7 days
- CT not diagnostic → Lumbar puncture (xanthochromia)
- CTA/ MRA (95%~100% >5mm) and 4 vessel angio for the aneurysm

Francis. J Headache Pain Manag. 2017

SAH - II



10 days after SAH
T2*-weighted

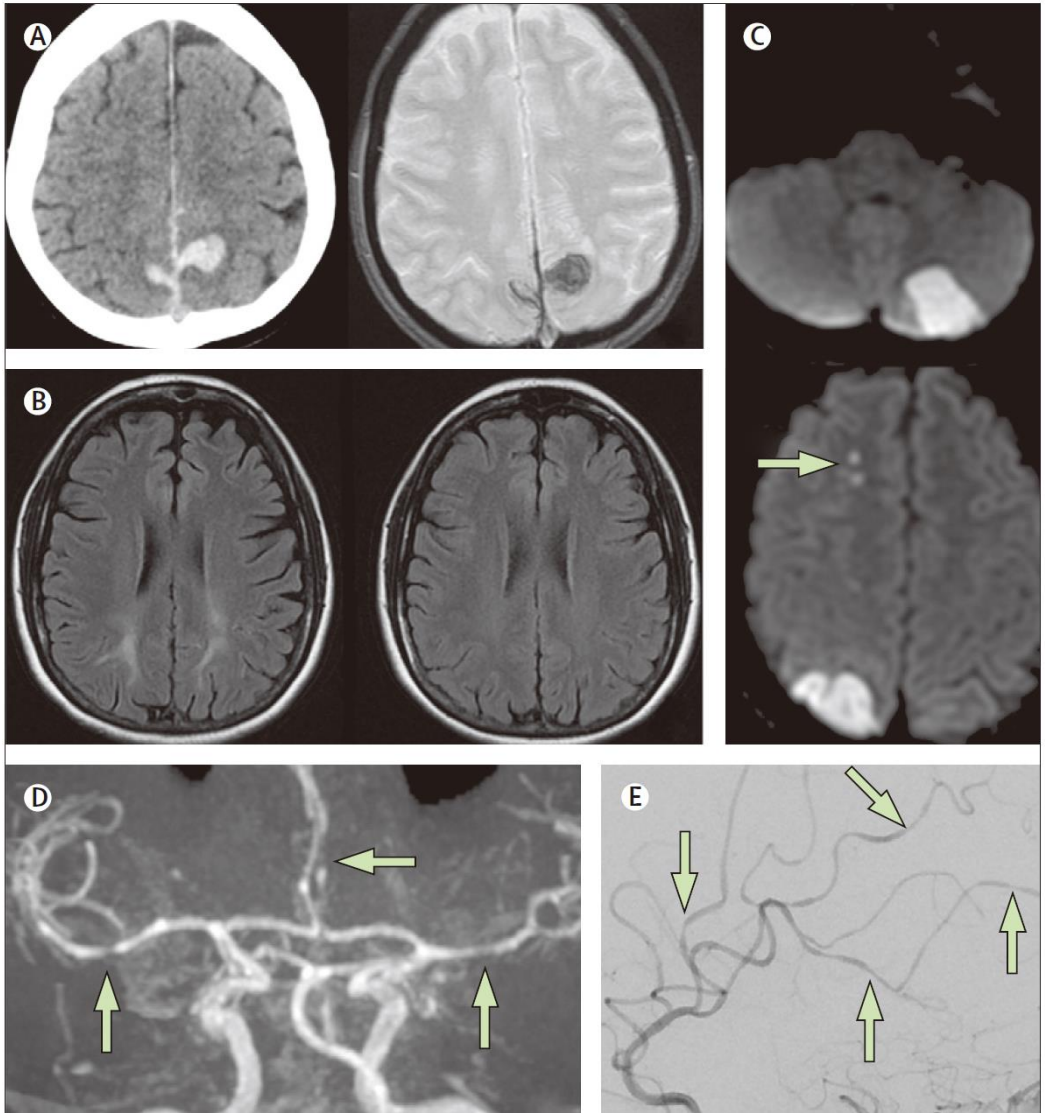


MRI (FLAIR, T2*):
3-14 d more sensitive than CT

Francis. J Headache Pain Manag. 2017

Reversible cerebral vasoconstriction syndrome (RCVS) - I

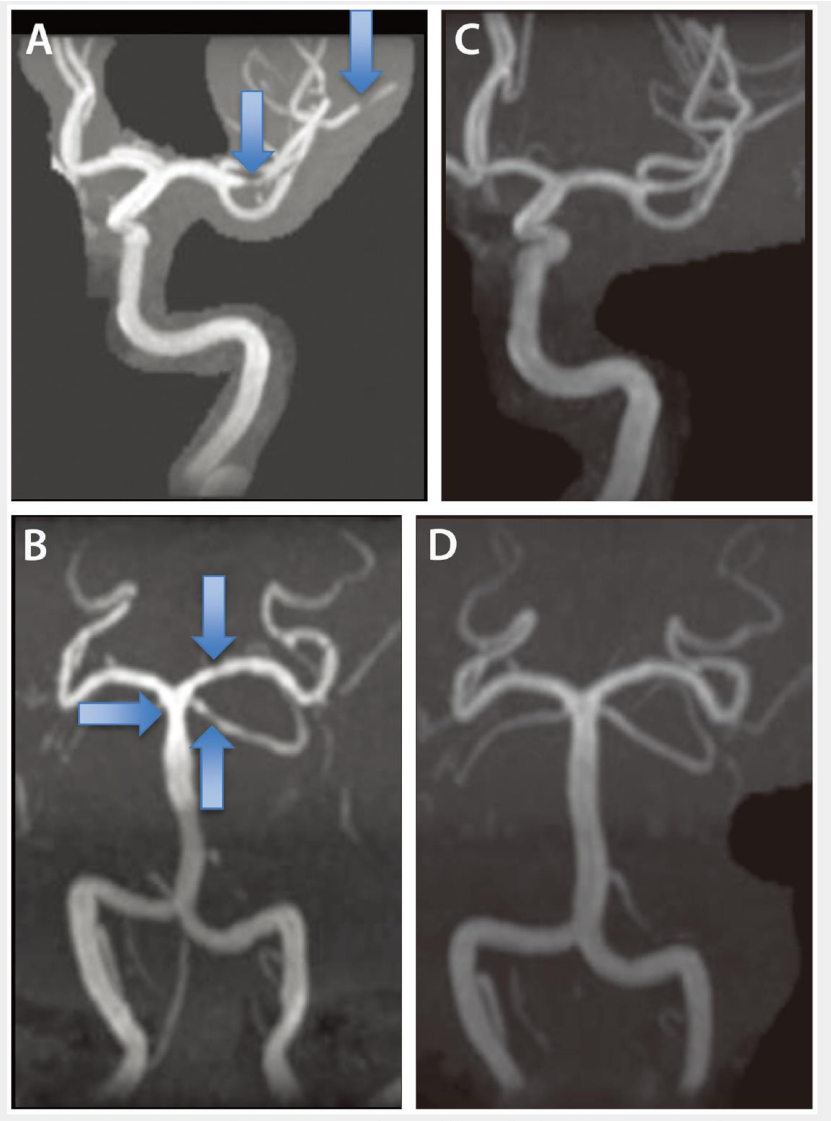
- Triggers in 80% of patients (emotion, sexual activity, exertion, coughing)
- Abnormal MRI (30-80%) : ICH, SAH, infarct, posterior reversible encephalopathy syndrome (PRES)
- MRA/ Angio: strings and beads appearance (can be normal during the 1st week → repeat)



Ducros. Lancet Neurol . 2012

RCVS - II

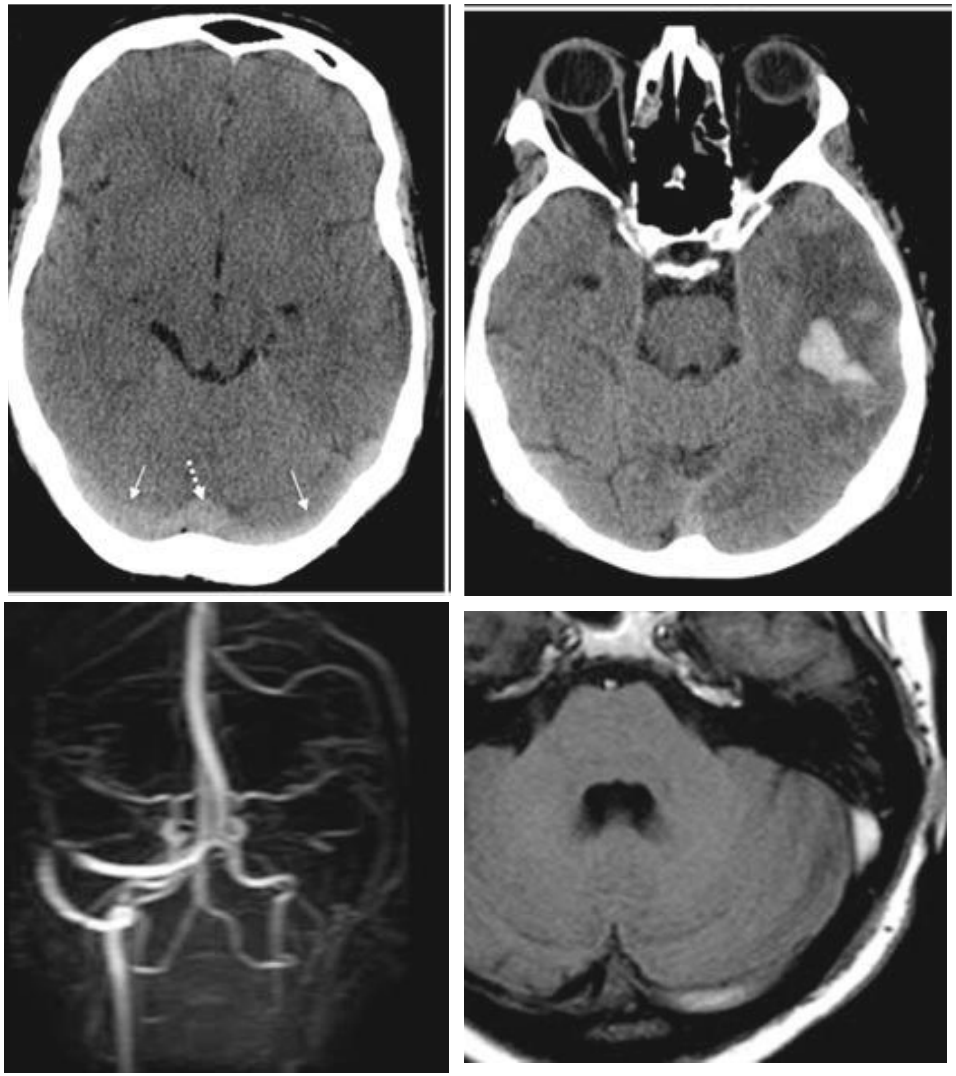
- Multiple TCH, bilateral (88%) and/or occipital regions (61%)
- Middle aged (49 y/o), female predominance (90%)
- Blood pressure surge: 39%
- PRES or stroke: 7%
- Nimodipine responsive
- Self-limited (3-4 weeks), resolution of vasoconstriction by 3 months (fulminant 5%–10%)



Chen et al. Neurology 2006; Yang et al. Expert Rev Neurother. 2018

Cerebral venous sinus thrombosis (CVST) - I

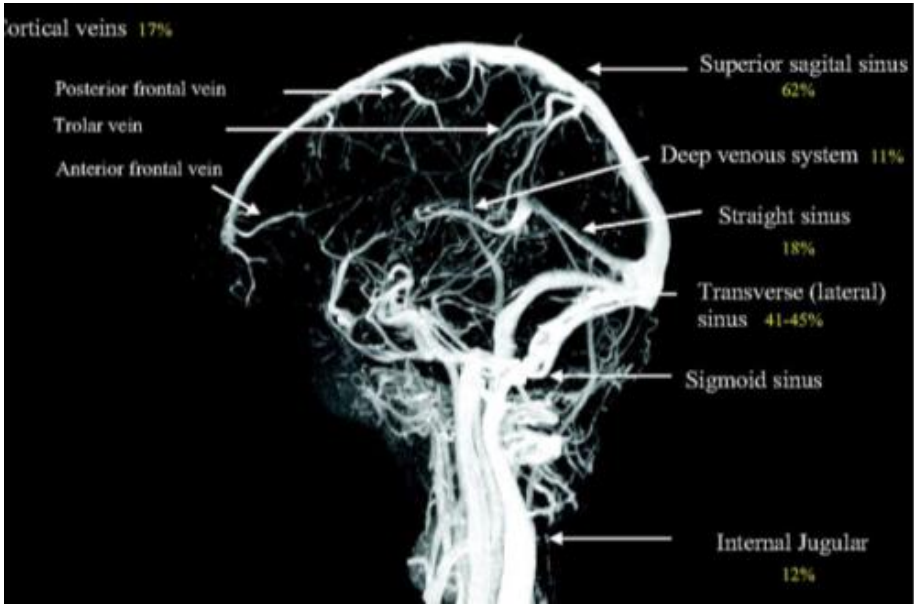
- Prothrombotics, contraceptives, pregnancy/puerperium, malignancy, infection, head injury
- Unknown: 12.5% to 33%
- Non contrast CT: Cord sign
- MRV (congenital or acquired)



Skeik et al. Vascular and Endovascular Surgery. 2012
Linn et al. Clinical Neuroradiology. 2010

CVST - II

MR sequence	Signal intensity	Acute stage (0–5 days)[b]	Subacute stage (6–15 days)[b]	Chronic stage (> 15 day)[b]
T1w	Hyperintense	30%	**71%**	39%
	Isointense	**68%**	29%	**54%**
	Hypointense	2%	0%	7%
T2w[a]	Hyperintense	25%	**52%**	**43%**
	Isointense	10%	32%	**45%**
	Hypointense	**65%**	16%	12%

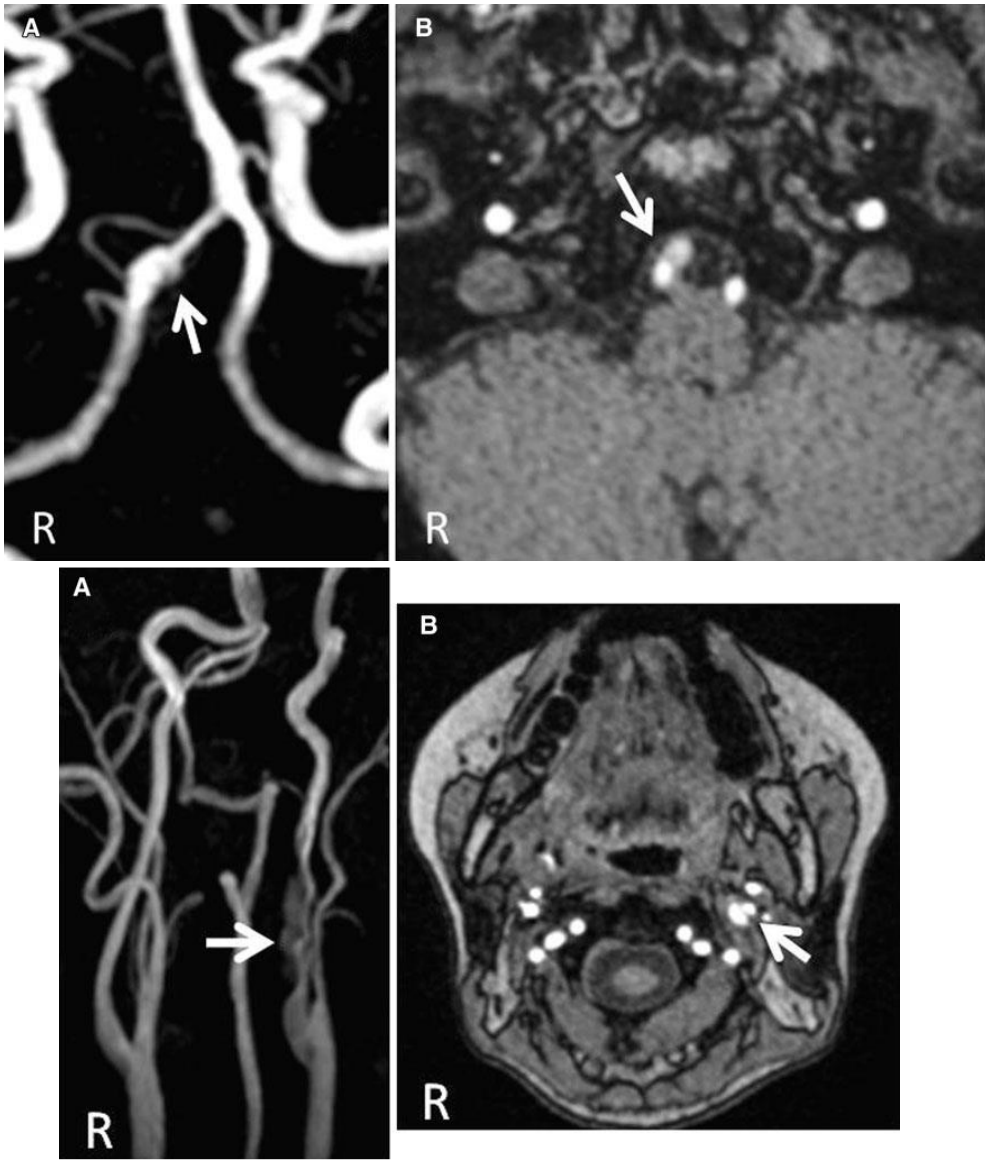


- A falsely negative MRI: very early or very late in the course (isointense)
- A false positive MRI: venous flow is slow but not thrombosed (MRV)
- Post contrast MRV/CTV: highly sensitive for absent or decreased venous flow

Skeik et al. Vascular and Endovascular Surgery. 2012
Linn et al. Clinical Neuroradiology. 2010

Cervicocephalic arterial dissection

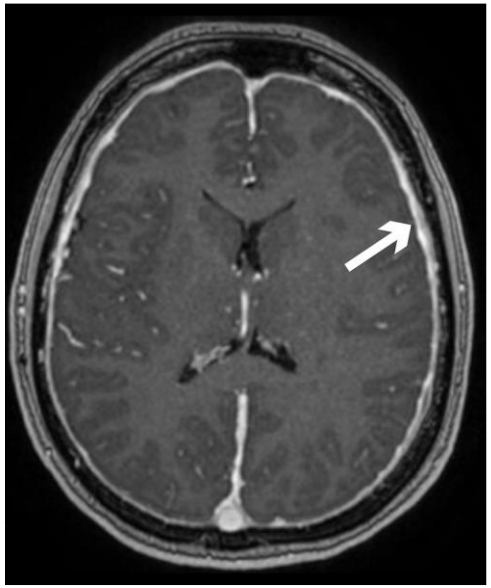
- Triggers: coughing, sneezing, exercise, manipulation
- Pain in the eye, neck or side of the head (carotid); back of the neck (vertebral)
- Carotid artery: ipsilateral Horner's syndrome, bruits
- MRA (source image), CTA
- Double lumen sign, String sign

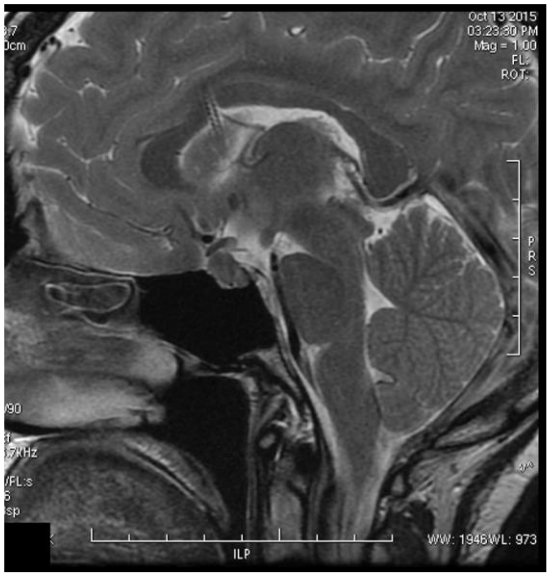


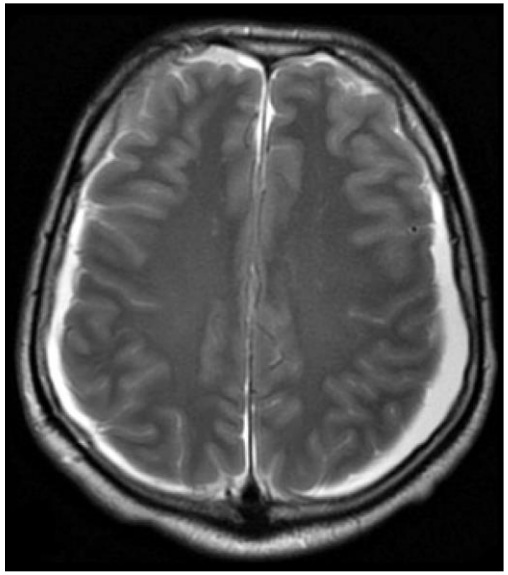
Maruyama et al. J Headache Pain. 2012

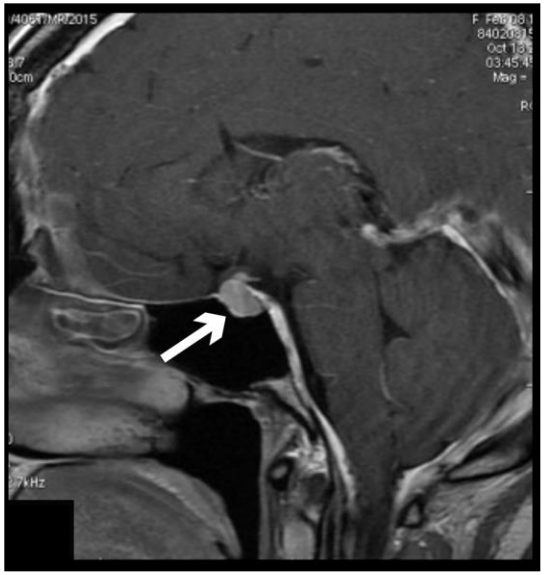
Intracranial hypotension - I

- Spontaneous intracranial hypotension vs. secondary
- Diffuse pachymeningeal enhancement
- Sagging of the brain (flattened pons, and inferior displacement of the 3rd Ventricle)
- Subdural fluid collections
- Pituitary enlargement









Michali-Stolarska et al. Pol J Radiol. 2017

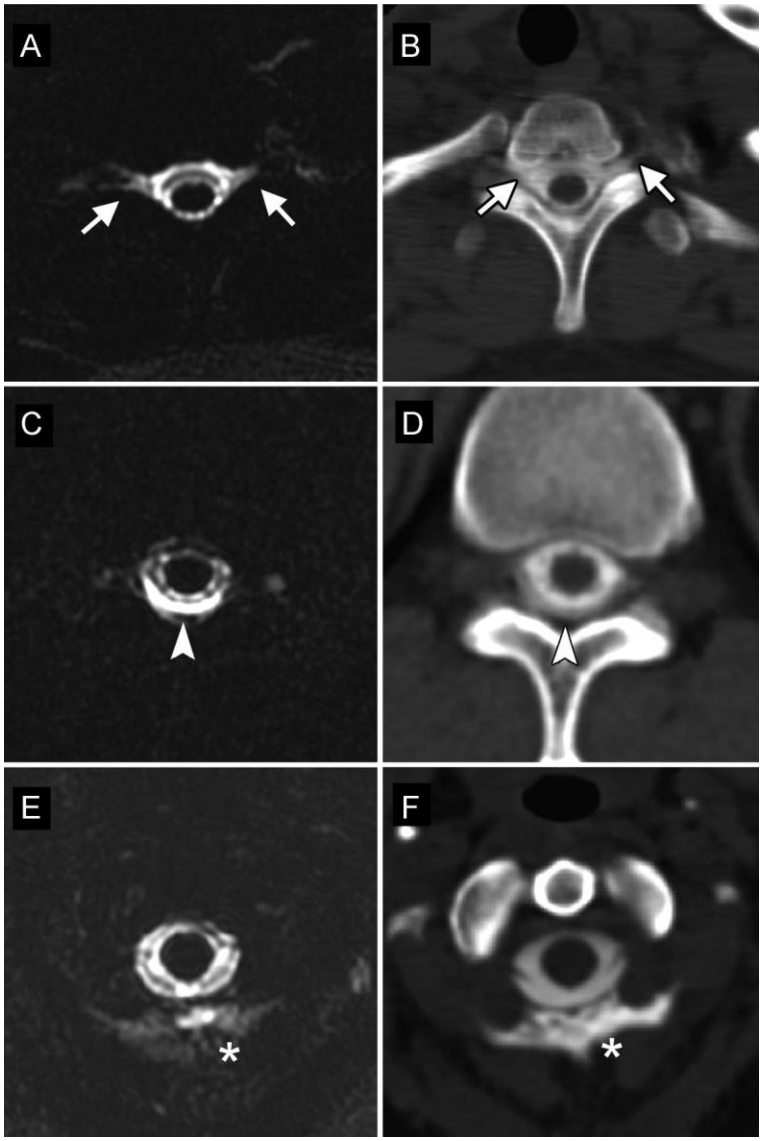
Intracranial hypotension - II

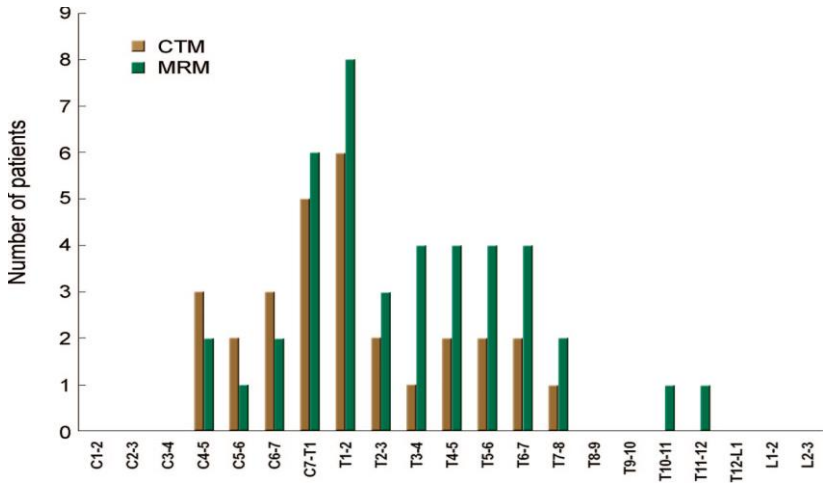
Heavily T2-weighted MRM CTM

Nerve roots

Epidural

Retro-spinal



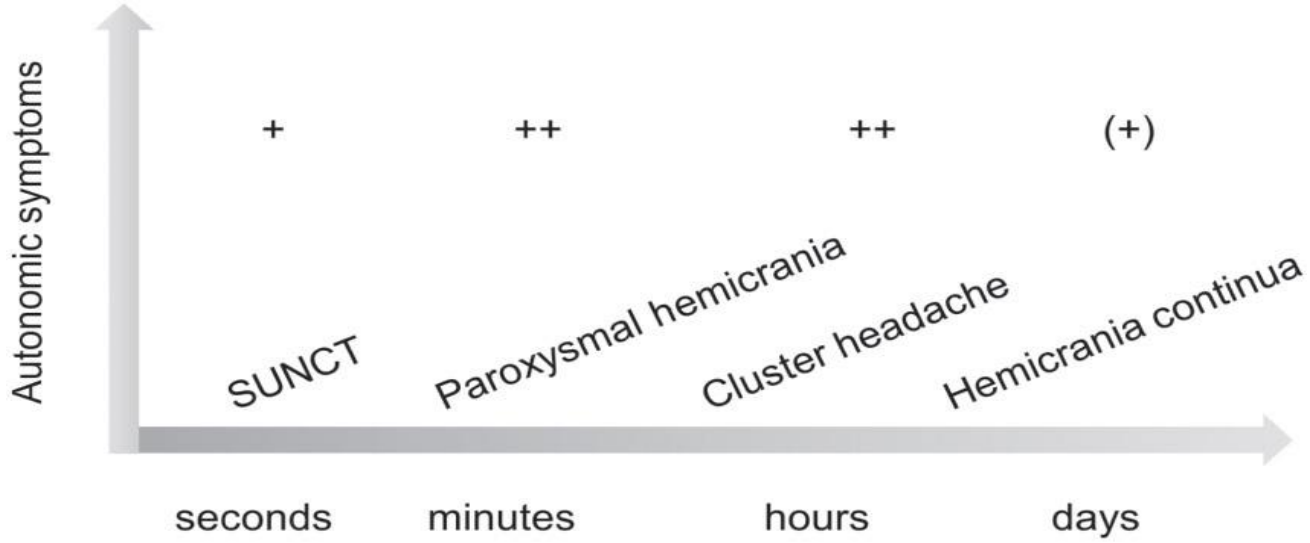


Epidural blood patch

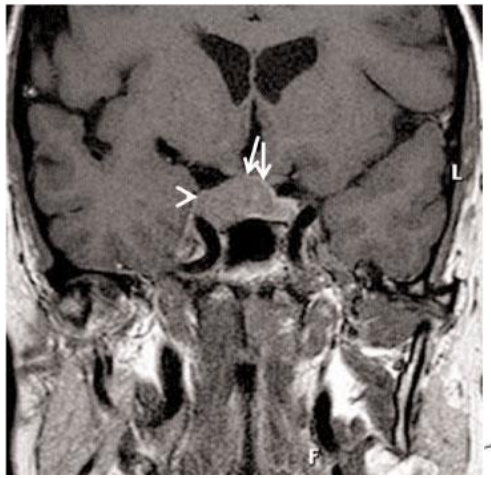
Wang et al. Neurology. 2009; *Kranz et al. AJR. 2016*

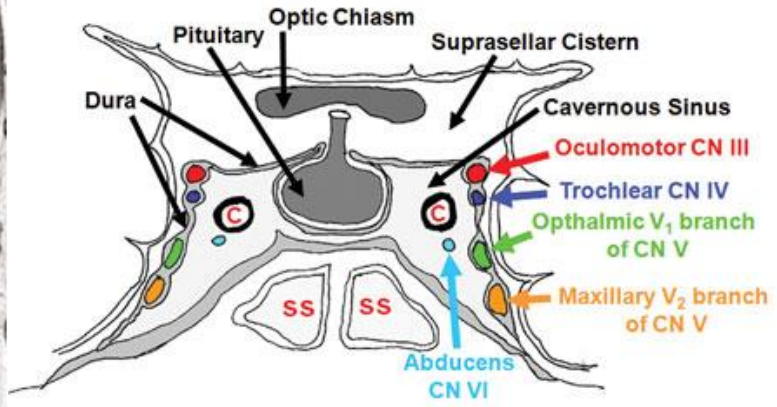
Trigeminal Autonomic Cephalalgias (TACs)

3.1 Cluster headache
3.2 Paroxysmal hemicrania
3.3 Short-lasting unilateral neuralgiform headache attacks
3.4 Hemicrania continua
3.5 Probable trigeminal autonomic cephalalgia



Should TACs Receive Image Studies?

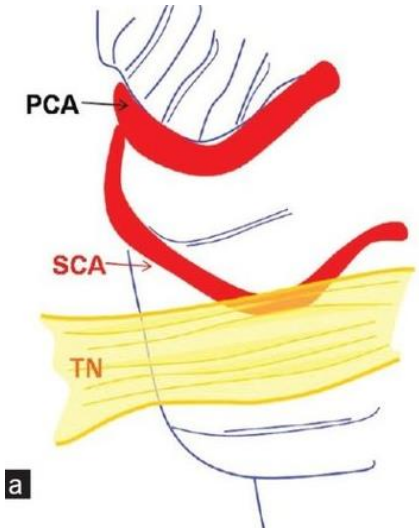


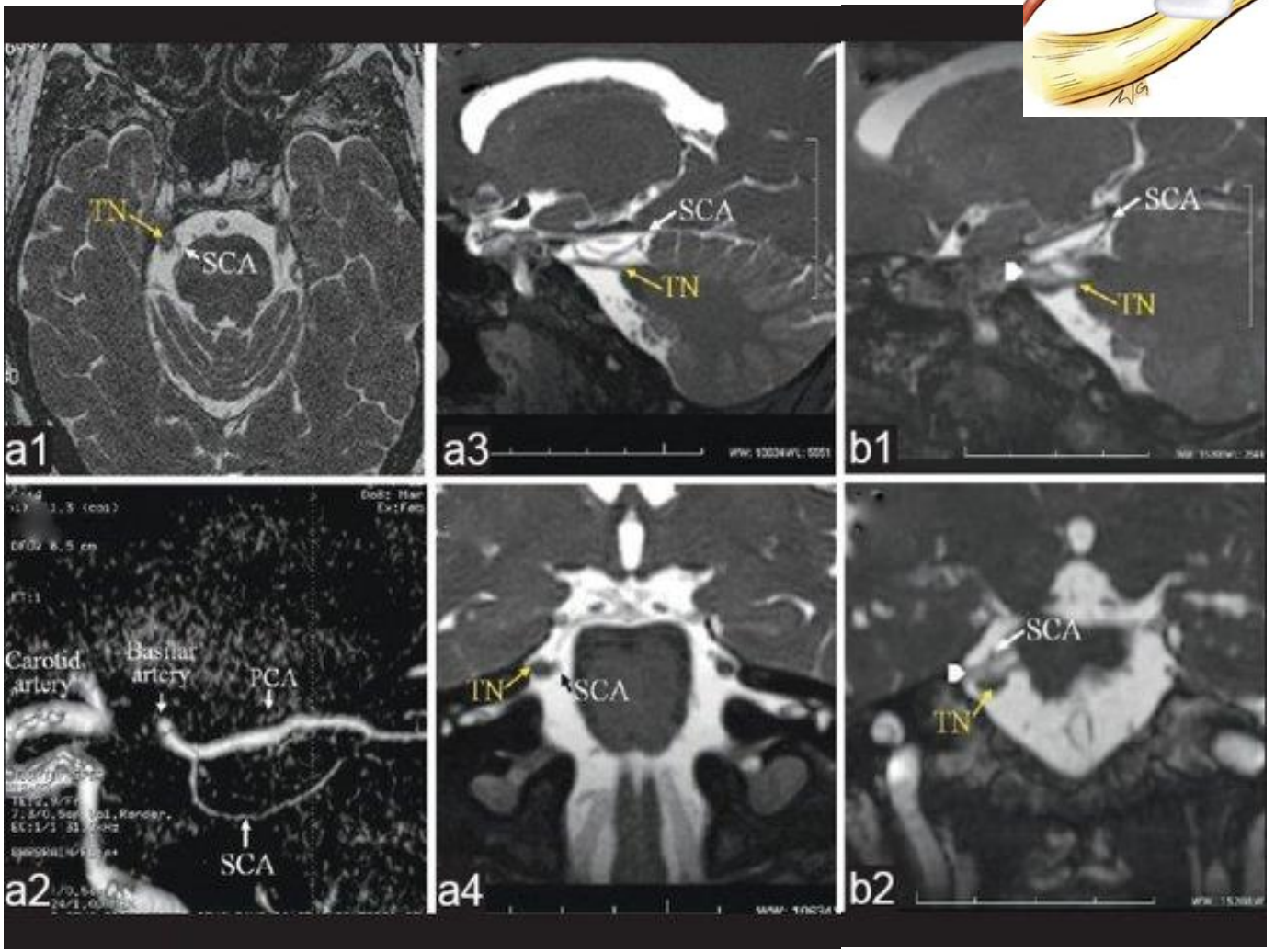


- More than 60% "Secondary" TACs cases
- Both intra/extra cranial neurovascular and structural lesions, esp. pituitary, carotid or cavernous sinus lesion.
- Additional imaging for assessing intracranial and cervical vasculature, the sellar and paranasal regions

Francis. J Headache Pain Manag. 2017
Wilbrink et al. Curr Opin Neurol. 2009

Trigeminal neuralgia - I

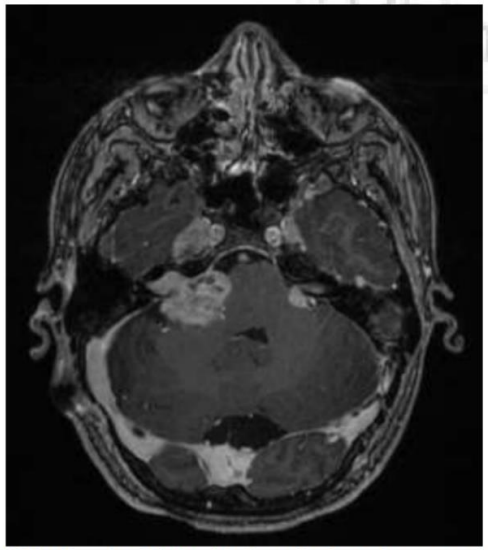




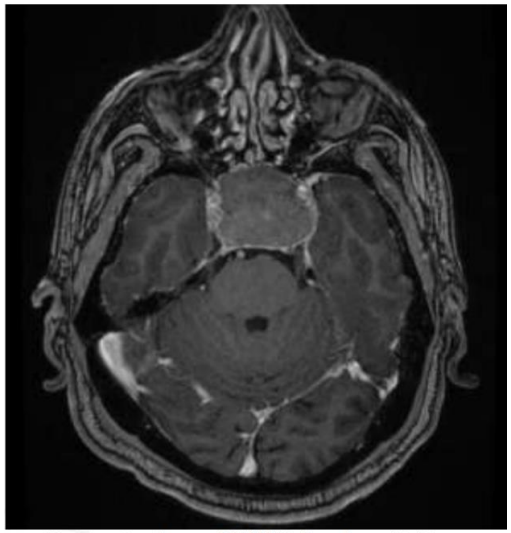
- Neurovascular compression: SCA
- High resolution: 3D FIESTA and TOF MRI scans (Teflon implant)

DeSouza et al. Front. Neuroanat. 2016; Prieto et al. Francis. Surg Neurol Int. 2012

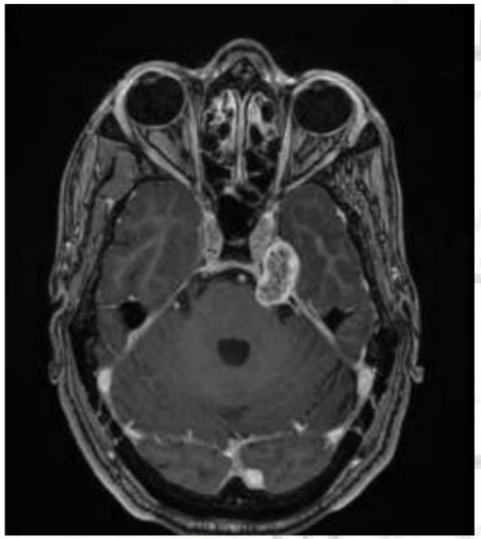
Trigeminal neuralgia - II



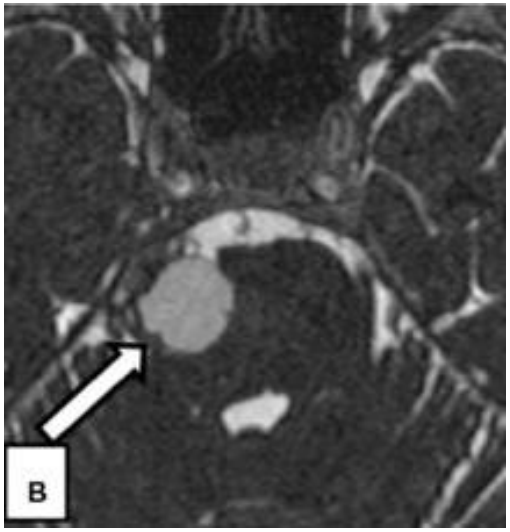
T1C+ showing Right sided vestibular schwannoma

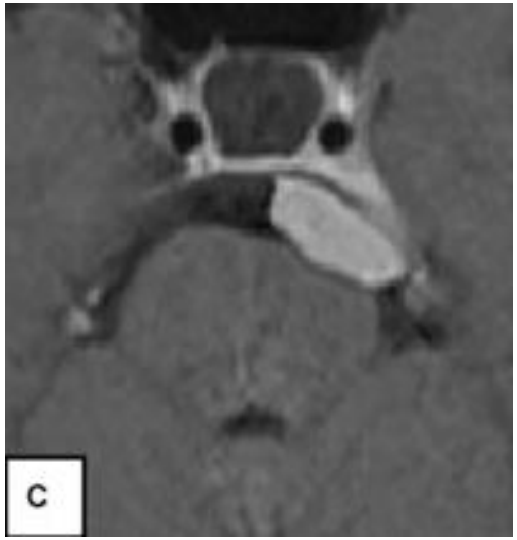


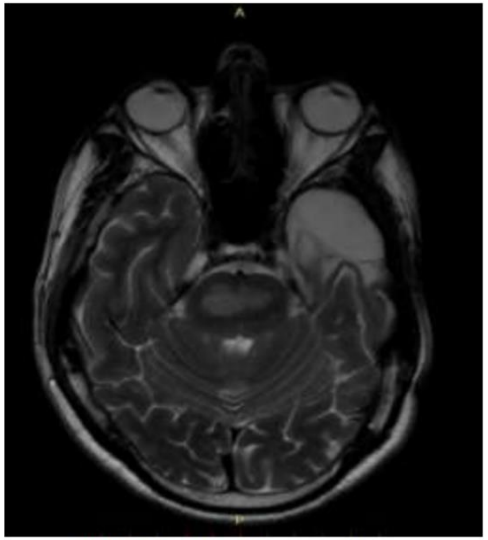
Contrast enhanced T1WI showing pituitary macroadenoma invading cavernous sinuses



Contrast enhanced T1WI showing hemangioma in left CP angle compressing left half of pons





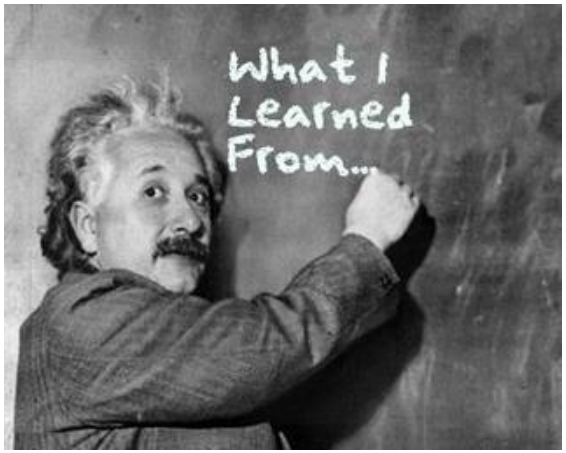


T2WI showing Pontine glioma

Geneidi et al. The Egyptian Journal of Radiology and Nuclear Medicine. 2016

Swetha et al. International Journal of Science and Research. 2018

Take home messages



Conclusion

- Migraine or tension headache (ICHD-3) rarely have abnormal imaging findings.
- If red flags or thunderclap headaches are present, neuroimaging must be considered.
- Evidence for the trigeminal autonomic cephalalgias or trigeminal neuralgia harbouring structural lesions.
- Investigation of patients with headache should be balanced against the risk of incidental (~0.5%).

Thanks for Your Attention !

E-mail :

fuji-yang@yahoo.com.tw

Since 2005

台灣頭痛學會

Taiwan Headache Society

Since 2005
台灣頭痛學會
Taiwan Headache Society

Migraine comorbidity: depression, anxiety and others

王署君 Shuu-Jiun Wang, MD
Brain Research Center and College of Medicine,
National Yang Ming Chiao Tung University
Neurological Institute, Taipei Veterans General Hospital
Taipei, Taiwan

April 11, 2021

陽明交大
NYCU

Disclosures

- Advisory boards of Eli Lilly, Taiwan Norvatis
- Speaker/moderator for AbbVie, Pfizer, Eli Lilly and Eisai
- PI of clinical trials
  - Eli-Lilly
  - AbbVie
  - Norvatis
- Research Grants:
  - Taiwan Minister of Technology and Science
  - Brain Research Center of National Yang Ming Chiao Tung University
  - Taipei Veterans General Hospital
  - Taiwan Headache Society

Clinical picture:

- **35-**year-old **female**, homemaker, BP **146/86 mmHg**, BMI=**33**
  - Daily headache for 5+ years
  - Headache onset at age 20
  - Daily use of Panadol-ES, Ergots or NSAIDs for 1 year
  - Tried >3 preventives without improvement
  - Daily use of BZDs for **sleep and anxiety**
  - **Dx of Major Depression and Fibromyalgia** for years

- 1 month ago, she visited a gastroenterologist for GI upset
  - Dx of Gastroesophageal reflux disease (GERD)
  - On esomeprazole (PPI) but **headache worsening** since then

Problem List:

- Headache worsening for one month
  - Chronic migraine
  - Medication-overuse headache
- Major depression, insomnia
- Hypertension, obesity, hyperlipidemia
- Fibromyalgia
- GERD

Comorbidity

- A ‘distinct **additional clinical entity**’ occurred during the clinical course of a patient having an index disease.

- Comorbidity vs. Co-existent disorders

Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis, 1970;23:455-468

Definition of “comorbidity” in medicine

- A medical condition existing simultaneously but **independently** with another condition in a patient

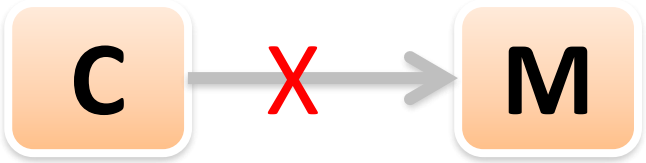
- A medical condition in a patient that **causes, is caused by, or is otherwise related to** another condition in the same patient

- Two or more medical conditions existing simultaneously **regardless of their causal relationship**.

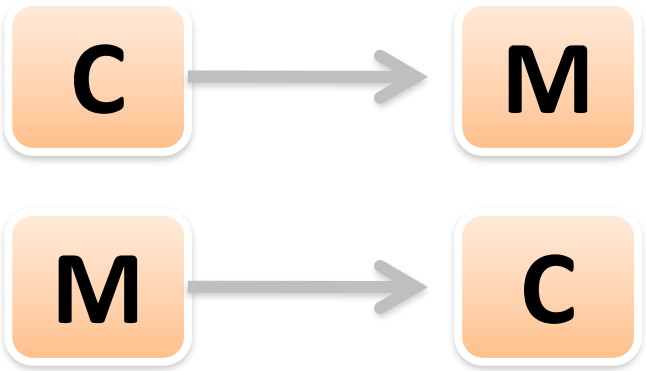
From WIKIPEDIA / The Free Encyclopedia

Possible explanations for comorbidity

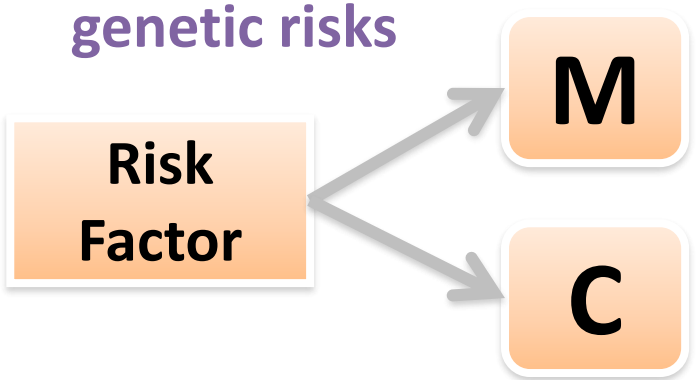
1. By coincidence of selection bias



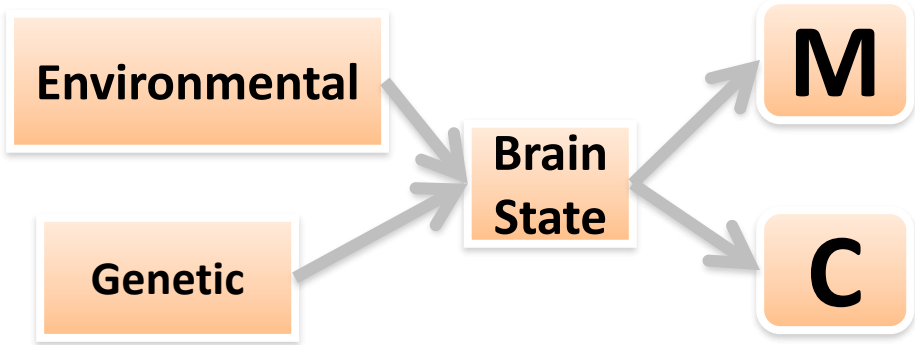
2. One condition may cause the other



3. Shared environmental or genetic risks



4. The risks produce brain state that gives rise to both



Lipton RB, Neurology 1994, 44(supp7) S4-5

Migraine/Depression: Neuro-limbic disorders Bidirectional Relationship

Migraine

RR=3.2

RR=3.1

Depression

Breslau N. et al.
Headache 1994;34:387-93

Clinical significance of comorbidity for migraine

- Comorbidity-associated management issues
  - Indications: two birds with one stone
  - Contraindications
- Higher disability
- Poorer health-related quality of life
- Higher chance of chronification
- Poorer outcomes

Avoid common errors of co-morbidity

- Co-morbidity dose not imply causation
- Co-morbidity does not influence the headache diagnosis
- Co-morbidity does not preclude treatment, but should guide treatment.

Health-related QOL

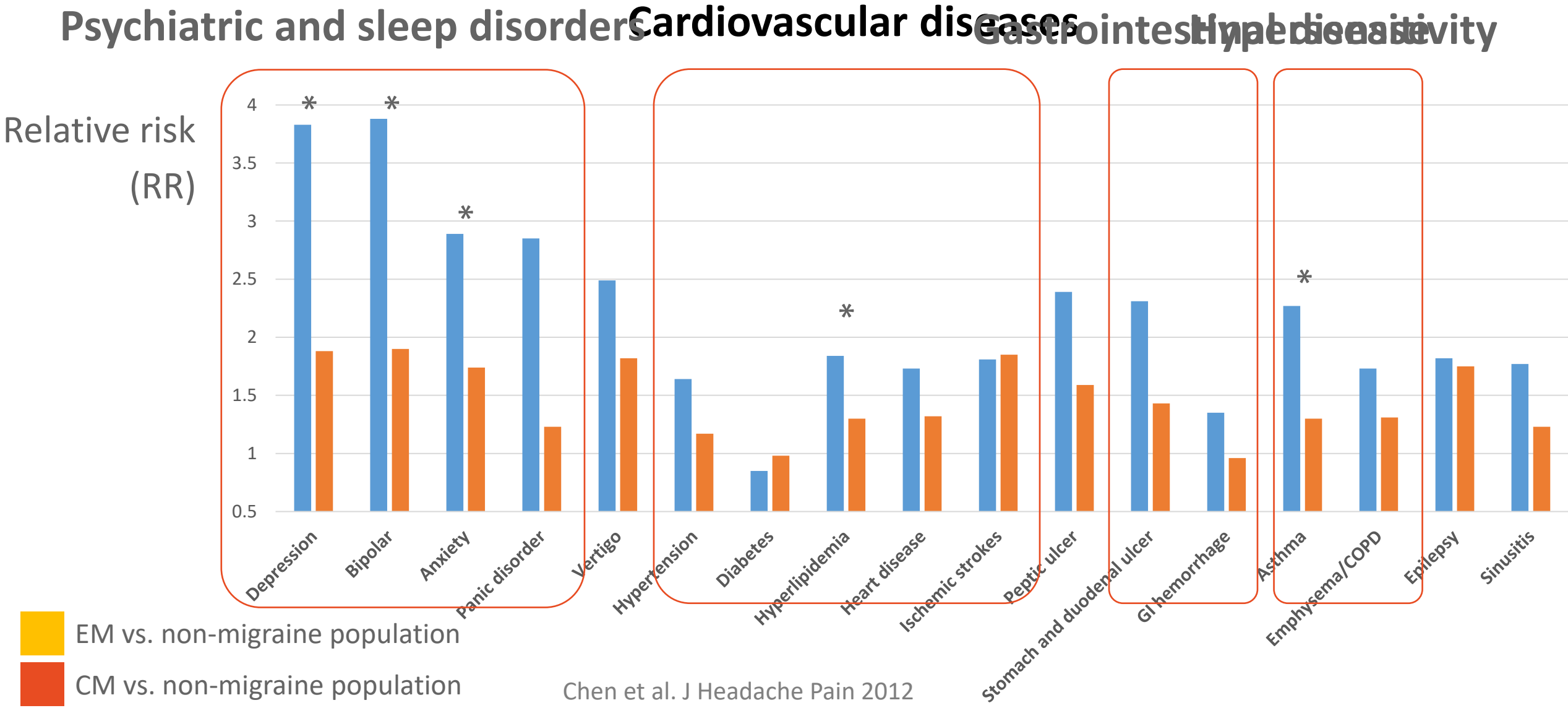
Migraine related

Migraine headache
Medication-related issues
Non-headache symptoms
-vestibular symptoms
-visual disturbance
-allodynia
-syncope…..

Migraine Comorbidity

Psychiatric disorders
Pain disorders
Sleep disorders
Cardiovascular disease
Gastroenterological disorders
Allergy…….

Comorbidities in CM and EM



Chen et al. J Headache Pain 2012

Psychiatric disorders

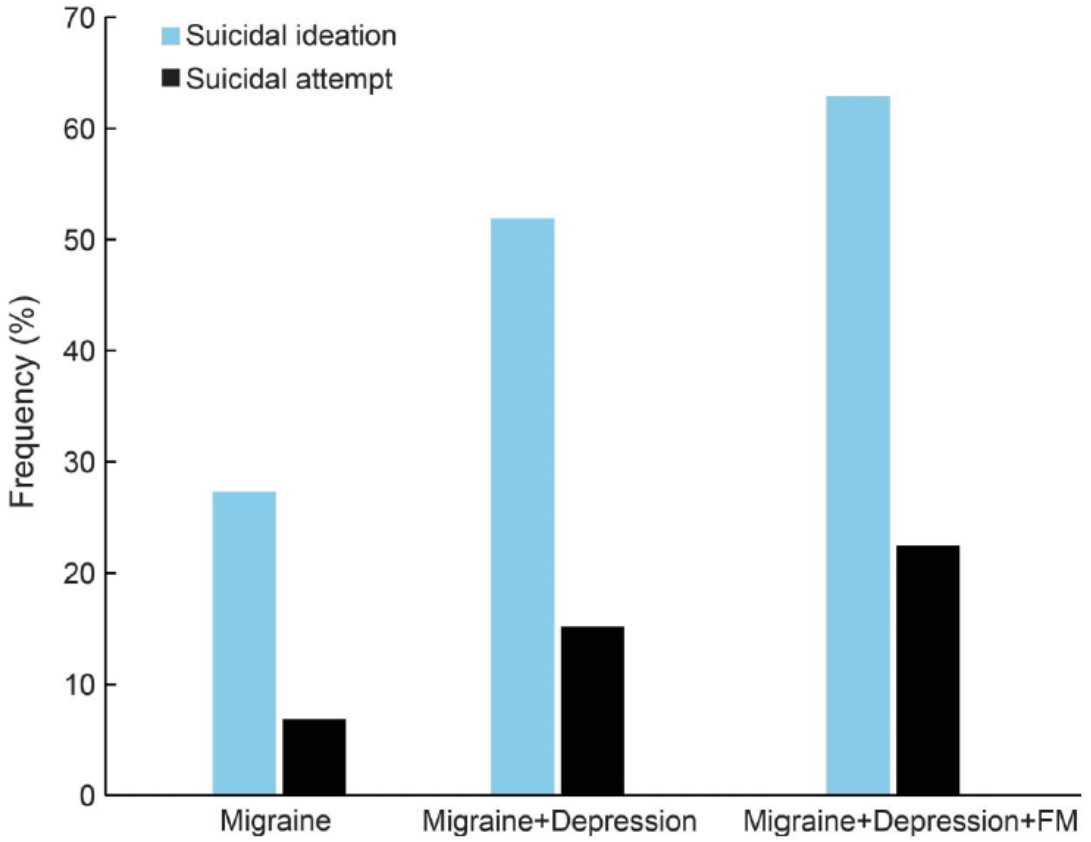
- More common in migraine patients, **esp. CM**
  - **Anxiety**: **5** times higher in migraineurs
  - **Depression**: **2-4** times higher in migraineurs
  - **Bipolar disorder**: **3.8** times higher in **CM**

Baskin, et al., Headache, 2006; Buse, et al., J Neurol., 2013; Chen, et al., J Headache Pain., 2012; Breslau, et al., Cephalalgia, 1998; Antonaci, et al., J Headache Pain., 2011; Breslau, et al., Neurol., 2003; Breslau, et al., J Psychiatr Res., 1993; Chen, et al., J Headache Pain., 2012.

Pain disorders

- **36%** of CM patients have FM
  - **Poor sleep** and **depression**
- Increased **suicide** risk in migraine patients with fibromyalgia

Figure Suicide risk in patients with migraine, migraine with comorbid depression, and migraine with comorbid depression and FM



Hudson, et al., Am J Med., 1992; Peres, et al., Neurol., 2001. Liu, et al., Neurol 2015

Sleep disorders

- Migraine patients have **worse** sleep quality vs. controls
- Sleep disorder, esp. snoring/sleep apnea
  - Is a risk factor of chronic migraine
  - It is modifiable!
- Restless leg syndrome (RLS)
  - **RLS** is associated with **disability in migraine**

Seidel, et al., Cephalalgia, 2009; Bigal, et al., Headache, 2006; Suzuki, et al., J Neurol., 2011

Obesity

- Obesity is positively associated with the prevalence of migraine
  - Esp. in women in reproductive age
  - Inconsistent reports
- In migraine patients,
  - Obesity is associated with higher migraine **frequency**
  - Obesity is a risk factor for **migraine chronification**

Ford, et al., Cephalalgia, 2008; Peterlin, et al., Headache, 2010; Bigal, et al., Arch Intern Med, 2007; Bigal, et al., Neurol., 2006.

Hypertension

- The association between migraine and HTN is inconsistent
- Positive studies:
  - **1.2 to 1.4** fold increased risk of developing HTN in migraine
- **BP control**
  - Anti-hypertensive agents: treat both HTN and migraine
    - Metoprolol, lisinopril, candesartan

 Entonen, et al., Eur J Public Health., 2014; Rist, et al., Cephalalgia, 2018.

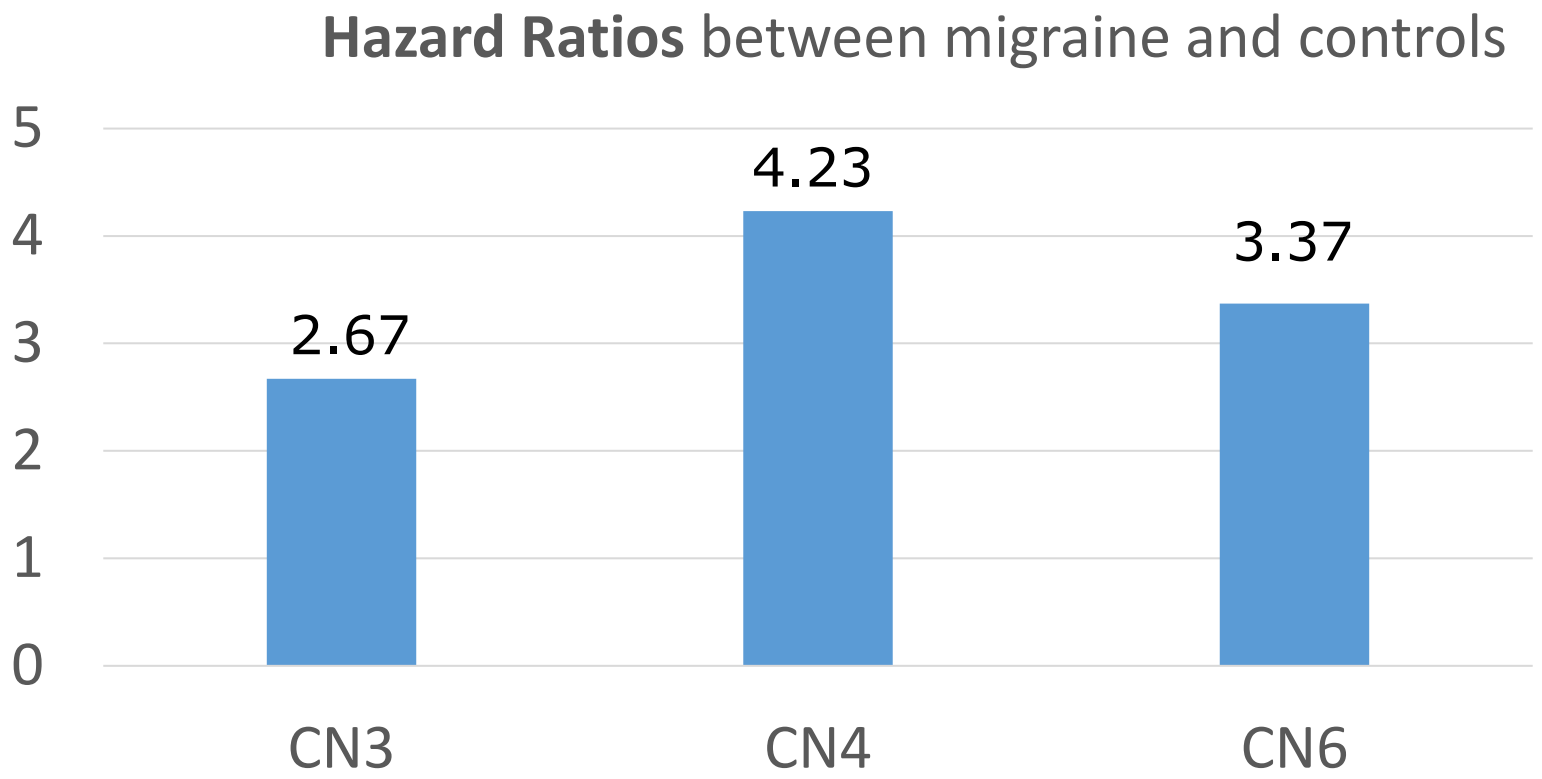
Stroke

- Have you ever asked a stroke patient if he/she has a history of migraine?
  - Ischemic stroke is associated with a **two-fold** risk of **migraine with aura** (MA)
  - No association between migraine without aura and stroke

Spector, et al., Am J Med., 2010.

Migraine and Risk of Ocular Motor Cranial Nerve Palsies

A Nationwide Cohort Study



Yang CP et al. Ophthalmology 2016;123:191-197

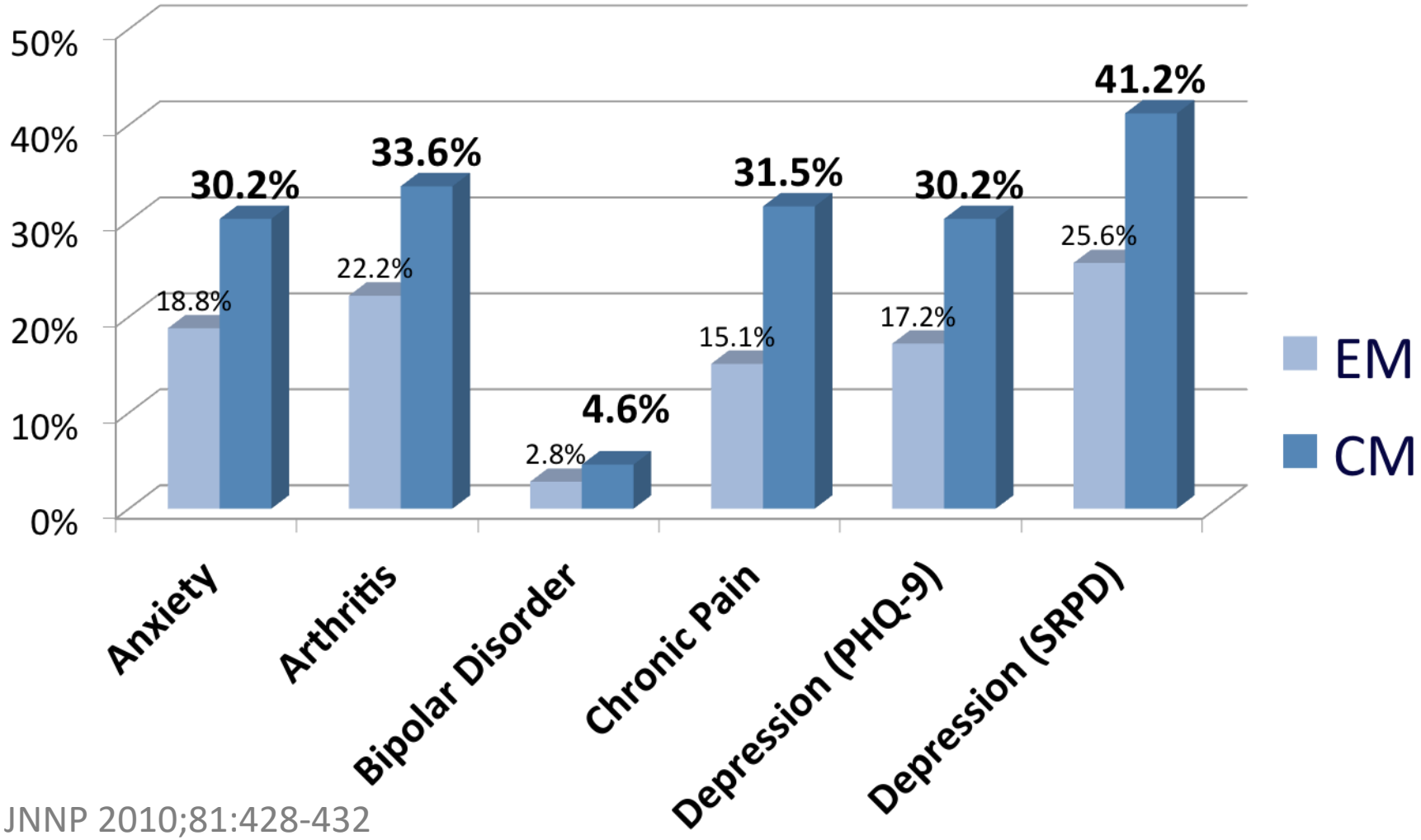
Headache severity / frequency and psychiatric disorders

High frequency headache → more likely to be depressed (Women's Health Study)

Headache frequency	Relative risk (95% CI) of **Incident depression**
No history of headache	1.00
< 6 times/yr	**1.35 (1.21, 1.50)**
Every other month	**1.62 (1.28, 2.05)**
Monthly	**1.45 (1.21, 1.74)**
Weekly or daily	**2.44 (1.85, 3.23)**

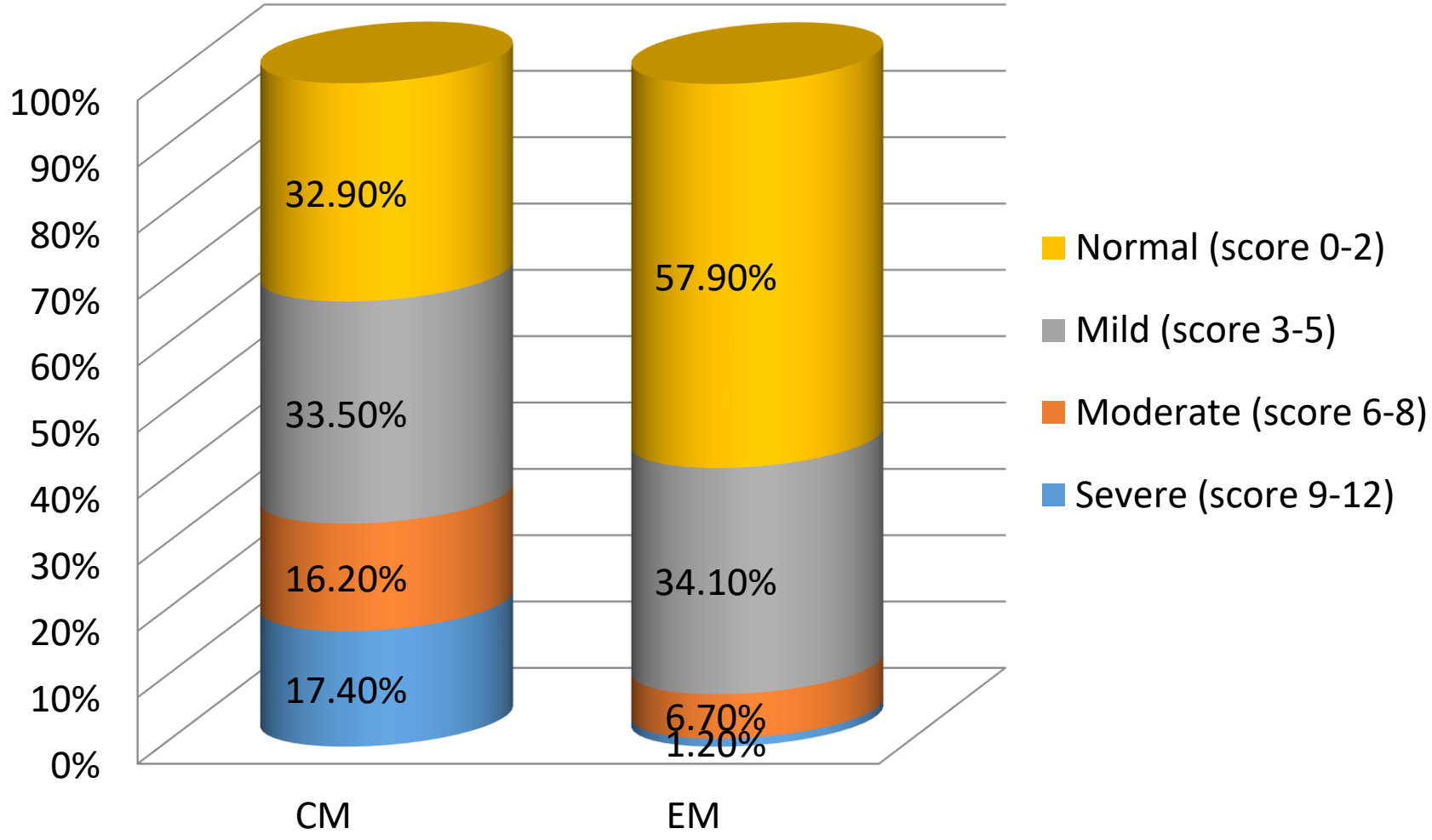
Rist et al. Cephalalgia 2013;33:1017–1025

Different psychiatric conditions in CM and EM:
AMPP Study (population-based study)



Buse et al. JNNP 2010;81:428-432

PHQ4 to measure the severity of depression and anxiety in patients with migraine



Wang SJ et al. Cephalalgia 2012;33: 171–181

Psychiatric comorbidities: is migraine with aura different?

Life-time psychiatric disorders and migraine

	Rate/100			AOR (95% CI)	
	No migraine ($n = 879$)	Migraine without aura ($n = 69$)	Migraine with aura ($n = 59$)	Migraine without aura vs. none	Migraine with aura vs. none
Major depression	9.0	21.7	32.2	2.2 (1.2- 4.0)	4.0 (2.2- 7.2)
Bipolar I	0.9	2.9	6.8	2.4 (0.5-11.3)	7.3 (2.2-24.6)
Bipolar II	0.8	2.9	5.1	2.5 (0.5-11.9)	5.2 (1.4-19.9)
Panic	1.8	5.8	17.0	3.0 (1.0- 9.4)	10.4 (4.5-24.1)
OCD	1.8	8.7	8.5	4.8 (1.8-12.7)	5.0 (1.8-14.6)
GAD	1.9	11.6	8.5	5.5 (2.3-13.2)	4.1 (1.4-11.5)
Phobia	20.6	34.8	45.8	1.8 (1.0- 3.0)	2.9 (1.7- 5.0)
Any anxiety	27.0	50.7	57.6	2.3 (1.3- 4.1)	3.1 (1.8- 5.3)
Nicotine dependence	18.2	34.8	30.5	2.3 (1.3- 3.8)	1.8 (1.0- 3.2)
Alcohol A/D	20.6	24.6	30.5	1.6 (0.9- 2.8)	2.1 (1.2- 3.9)
Illicit drug A/D	10.4	14.5	27.1	1.6 (0.8- 3.3)	3.9 (2.1- 7.3)

Note. AOR = adjusted odds ratio, adjusted for respondents' sex. CI = confidence interval. OCD = obsessive-compulsive disorder. GAD = generalized anxiety disorder. A/D = abuse or dependence.

Breslau N et al. Psychiatr Res 1991;37:11-23

Depression in migraine and other headache Women's Health Study

Headache Status	Relative risk (95% CI) of **incident depression**
No history of headache	1.00
History of non-migraine headache	**1.43 (1.31, 1.56)**
Migraine with aura	**1.51 (1.33, 1.71)**
Migraine without aura	**1.38 (1.24, 1.54)**
Past history of migraine	**1.53 (1.35, 1.74)**

Rist et al. Cephalalgia 2013;33:1017–1025

Psychiatric comorbidity in adolescents with CDH : migraine with aura might be worse

	OR for MO	OR for MA
Depressive disorders	2.1	**4.1***
Major depression	4.2*	**13.9***
Dysthymia	0.9	0
Anxiety disorders	3.7*	**4.6***
Panic disorder	6.4*	**10.3***
Social phobia	∞	∞
Obsessive compulsive disorder	3.0	**8.0***
General anxiety disorder	1.3	2.2
≧1 psychiatric comorbidity	3.4*	**4.5***
High suicidal risk (score ≧ 10)	2.1	**7.8***

aOR: adjusted odds ratio, * p<0.05

Wang et al. Neurology 2007; 68:1468-1473

Life-time suicide attempts and migraine 21-30 years old in HMO, Detroit (n=1,007)

	Attempted suicide rate/100			RR (95% CI)	
	No Migraine	Migraine without aura	Migraine with aura	Migraine without aura vs. none	Migraine with aura vs. none
Males	2.2	7.1	15.4	3.2 (0.4-23.8)	6.9 (1.6-29.3)
Females	4.6	10.9	23.9	2.4 (1.0- 5.5)	5.2 (2.7- 9.9)

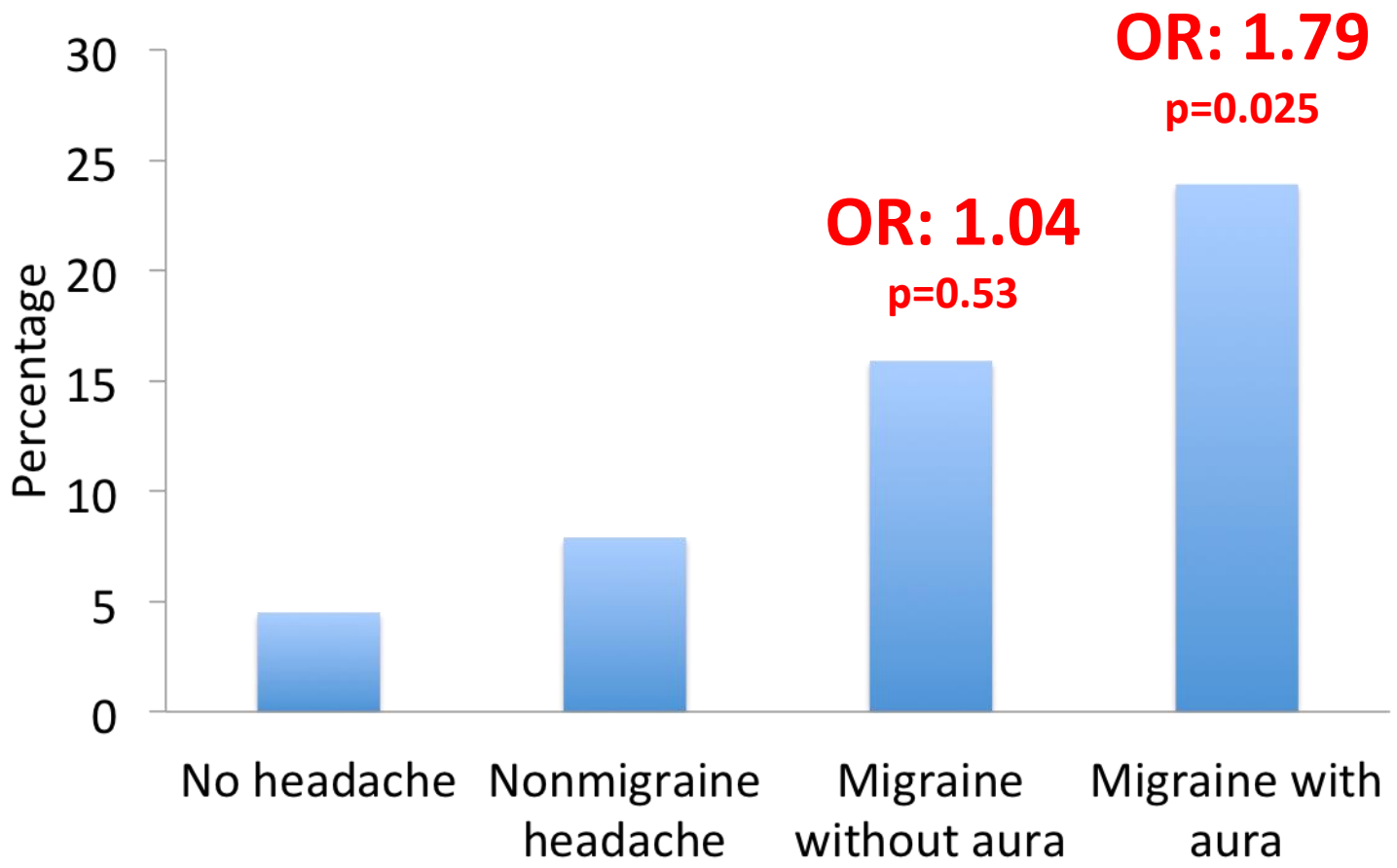
Note. RR (95% CI) = relative risk for suicide attempts, 95% confidence interval.

	Logistic odds	Odds ratio	95% confidence interval
Migraine without aura	0.46	1.59	0.63- 4.01
Migraine with aura	1.09	2.99	1.35- 6.61
Major depression	1.69	5.45	2.86-10.38
Other disorders[1]	0.99	2.68	1.25- 5.75
Sex (female)	0.64	1.90	0.93- 3.90

1. Affective disorders, anxiety disorders, and substance use disorders.

Breslau N et al. Psychiatr Res 1991;37:11-23

Suicidal ideation in young adolescents (age 13-15, n=3,963) with migraine



Wang et al. Neurology. 2009;72:1146–52.

Suicide attempt in migraine and non-migraine severe headache (2-year FU)

	Suicide attempt	OR(95%CI)	Model 1	Model 2	Model 3
Migraine N=496	**8.7%**	**7.21 (3.21-16.2)**	**7.07 (3.15- 15.9)**	**4.59 (2.00- 10.5)**	**4.43 (1.93- 10.2)**
Severe Headache N=151	**9.9%**	**8.30 (3.35-21)**	**8.89 (3.54- 22.3)**	**6.14 (2.40- 15.8)**	**6.20 (2.40- 16.0)**
Control N=539	**1.3%**	**Ref=1**			

Model 1: Adjusting statistically for sex
Model 2: Adjusting model 1 and additionally for major depression and any anxiety
Model 3: Adjusting model 2 and additionally for history of suicide attempt at baseline

Breslau N et al. Headache 2012;52:723-731

Suicide Attempt in MA (n=151) and MoA (n=345)

- MA
  - major depression (P = .008)
  - anxiety disorder (P = .010)
- 2-year cumulative rate of suicide attempt
  - Unadjusted:

    MA vs. MoA: **OR=2.1** (95% CI 1.1-4.0) (P = .019).
  - Adjusted depression/anxiety disorder:

    MA vs. MoA: **adjusted OR=1.7** (95% CI 0.9- 3.3) (P = .095)

Breslau N et al. Headache 2012;52:723-731

Possible Mechanisms : Comorbid Depression/Anxiety in patients with migraine

- Depression/Anxiety and migraine share common mechanisms
  - ***Serotonergic Dysfunction*** in Migraine and *Affective Disorder*
  - Hypothalamic pituitary adrenal ***(HPA) dysfunction***
- Diagnostic overlap
  - Transdiagnostic symptoms

Merikangas et al. Arch Gen Psychiatry 1990;47:849-53
Merikangas et al. J Psychiat Res1993;27:189-210
Breslau et al. Headache 1994;34:387-93
Breslau et al. Neurology 2000;54:308-13
Sheftell and Atlas. Headache 2002;42:934-44

Original Article

Cephalalgia
An International Journal of Headache

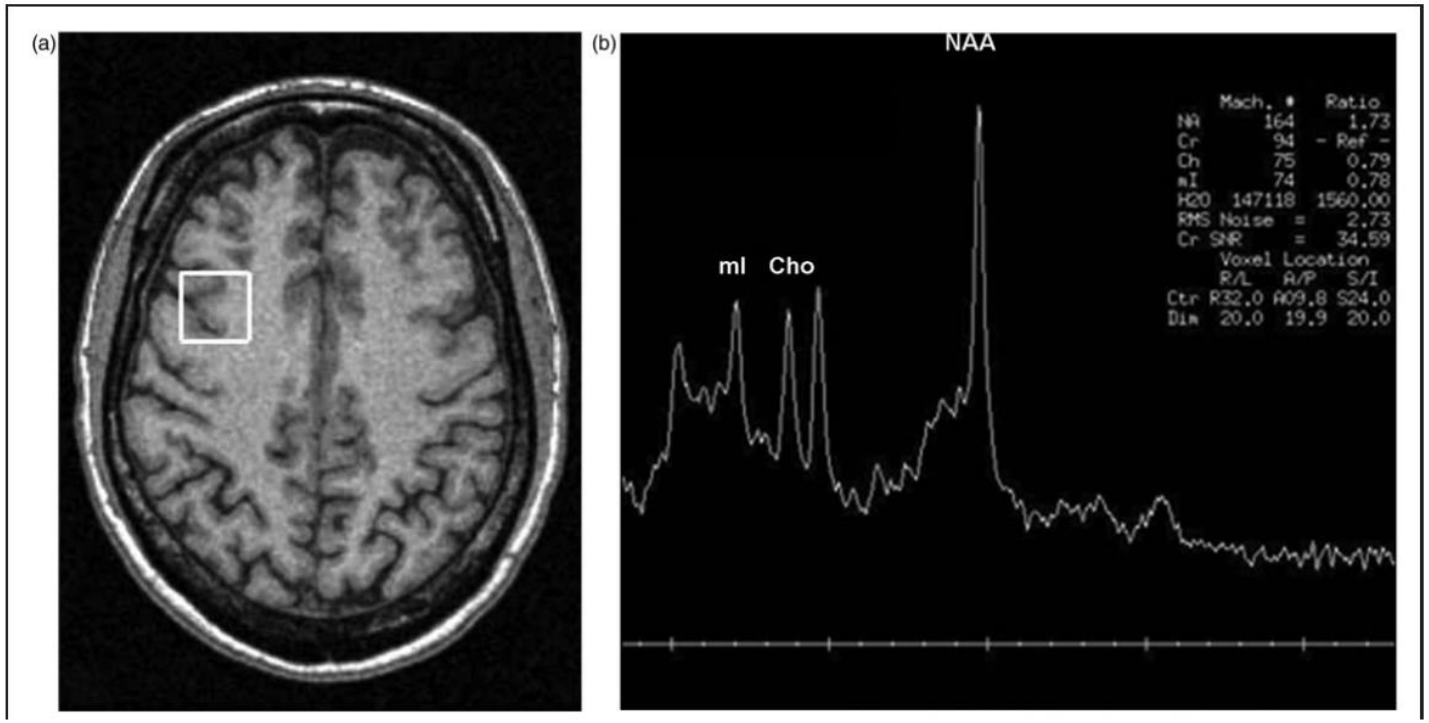
International Headache Society

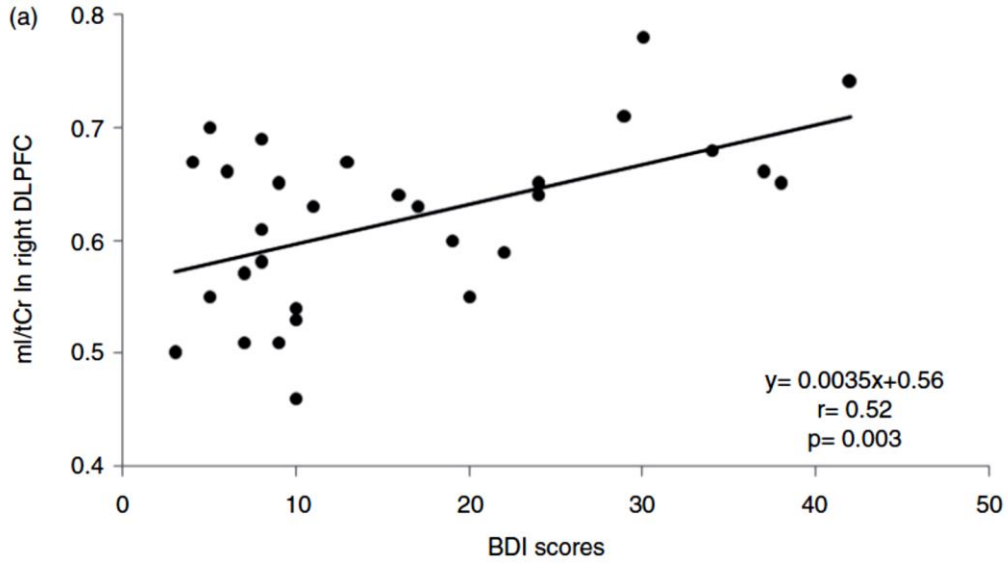
Increased myo-inositol level in dorsolateral prefrontal cortex in migraine patients with major depression

Cephalalgia
2015, Vol. 35(8) 702–709

DOI: 10.1177/0333102414557048
cep.sagepub.com

SAGE





Lirng JF, et al. Cephalalgia 2015;35:702-9.

Possible negative consequences of screening for psychiatric co-morbidity

- Patients may feel stigmatized.
- Recognition of a psychiatric disorder may dissuade the clinician from adequately addressing the headache disorder.
- Excessive costs of time and money (e.g., purchasing screening measures) for patient and clinician.
- Identification of psychiatric disorders may be harmful if appropriate follow-up treatment is not provided.
- Clinicians may incorrectly diagnose a psychiatric disorder based on a positive screen, without appropriate confirmation.
- Clinicians may prescribe unnecessary medications based on an unconfirmed positive screen.

Reasons to screen for psychiatric co-morbidity in headache patients

- The presence of anxiety and/or depression may significantly impact headache prognosis and satisfaction with headache treatment, and is associated with increased headache-related disability.
- Anxiety and/or depression may yield differential response to headache prophylaxis.
- Anxiety and/or depression may suggest preferential use of psychotropics to treat the comorbid disorders.
- Anxiety and/or depression may influence compliance with mediation and behavioral treatment, as well as the tendency to experience and report medication side effects.
- Anxiety and/or depression have significant impact on quality-of-life and health care utilization, regardless their impact on headache.
- The use of antidepressants may trigger mania in a patient with unrecognized bipolar disorder.
- Patients with bipolar disorder and/or a history of chemical dependency may have a tendency to medication overuse or drug-seeking behavior.
- The recognition of psychiatric comorbidity may be a key component in developing a therapeutic doctor-patient relationship.
- The use of screening tools may improve the patient's recognition of, and attention to, relevant psychiatric factors.
- Screening tools may be useful in excluding a suspected psychiatric disorder whose presentation suggests a psychiatric basis for somatic complaints.

Roche | Beck Depression Inventory | Baseline

V 0477 CRTN: ____ CRF number: ____ Page 14 patient inits: ____

BDI-II Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

Subtotal Page 1

Continued on Back

THE PSYCHOLOGICAL CORPORATION® Harcourt Brace & Company SAN ANTONIO
Orlando • Boston • New York • Chicago • San Francisco • Atlanta • Dallas
San Diego • Philadelphia • Austin • Fort Worth • Toronto • London • Sydney

0154018392
NR15645

Roche | Beck Depression Inventory | Baseline

V 0477 CRTN: ____ CRF number: ____ Page 15 patient inits: ____

11. Agitation
- 0 I am no more restless or wound up than usual.
- 1 I feel more restless or wound up than usual.
- 2 I am so restless or agitated that it's hard to stay still.
- 3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest
- 0 I have not lost interest in other people or activities.
- 1 I am less interested in other people or things than before.
- 2 I have lost most of my interest in other people or things.
- 3 It's hard to get interested in anything.

13. Indecisiveness
- 0 I make decisions about as well as ever.
- 1 I find it more difficult to make decisions than usual.
- 2 I have much greater difficulty in making decisions than I used to.
- 3 I have trouble making any decisions.

14. Worthlessness
- 0 I do not feel I am worthless.
- 1 I don't consider myself as worthwhile and useful as I used to.
- 2 I feel more worthless as compared to other people.
- 3 I feel utterly worthless.

15. Loss of Energy
- 0 I have as much energy as ever.
- 1 I have less energy than I used to have.
- 2 I don't have enough energy to do very much.
- 3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern
- 0 I have not experienced any change in my sleeping pattern.
- 1a I sleep somewhat more than usual.
- 1b I sleep somewhat less than usual.
- 2a I sleep a lot more than usual.
- 2b I sleep a lot less than usual.
- 3a I sleep most of the day.
- 3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability
- 0 I am no more irritable than usual.
- 1 I am more irritable than usual.
- 2 I am much more irritable than usual.
- 3 I am irritable all the time.

18. Changes in Appetite
- 0 I have not experienced any change in my appetite.
- 1a My appetite is somewhat less than usual.
- 1b My appetite is somewhat greater than usual.
- 2a My appetite is much less than before.
- 2b My appetite is much greater than usual.
- 3a I have no appetite at all.
- 3b I crave food all the time.

19. Concentration Difficulty
- 0 I can concentrate as well as ever.
- 1 I can't concentrate as well as usual.
- 2 It's hard to keep my mind on anything for very long.
- 3 I find I can't concentrate on anything.

20. Tiredness or Fatigue
- 0 I am no more tired or fatigued than usual.
- 1 I get more tired or fatigued more easily than usual.
- 2 I am too tired or fatigued to do a lot of the things I used to do.
- 3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex
- 0 I have not noticed any recent change in my interest in sex.
- 1 I am less interested in sex than I used to be.
- 2 I am much less interested in sex now.
- 3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

Subtotal Page 2

Subtotal Page 1

Total Score

NR15645

BDI>=10
BDI 19+
BDI 29+

Screening for depression but not **anxiety** is like taking a systolic BP but not a diastolic…

- They are closely interlinked.
- They both influence outcomes and HRQoL
- They both merit treatment
- Pharmacologic approaches are similar but have some important differences

Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'

Hospital Anxiety Depression Scale

Screen for both anxiety and depression

Positive: 10 or more

Verbal screening for psychiatric co-morbidity

- Direct questions
  - Are you depressed? (depression)
  - Are you a worrier? (anxiety)
- Indirect questions
  - How is your sleep/energy/mood?
  - What do you do for fun?

Treatment consideration for migraine preventive agents

AAN consensus on migraine preventives

Level A. Medications with established efficacy

- Antiepileptic drugs (AEDs):
  - Divalproex sodium
  - Sodium valproate
  - Topiramate (AE with depression)
- β-Blockers:
  - Metoprolol
  - Propranolol (Possible AE with depression)
  - Timolol
- Flunarizine (not available in the US) (AE with depression)
- Triptans: frovatriptan for short-term MAMs prevention
- New treatments: Botox, CGRP mAbs, gepants

Silberstein et al. Neurology 2012;78:1337-45

Level B. Medications are probably effective

- Antidepressants
  - Amitriptyline
  - Venlafaxine
- β-Blockers
  - Atenolol
  - Nadolol
- Triptans: naratriptan, zolmitriptan for short-term MAMs prevention

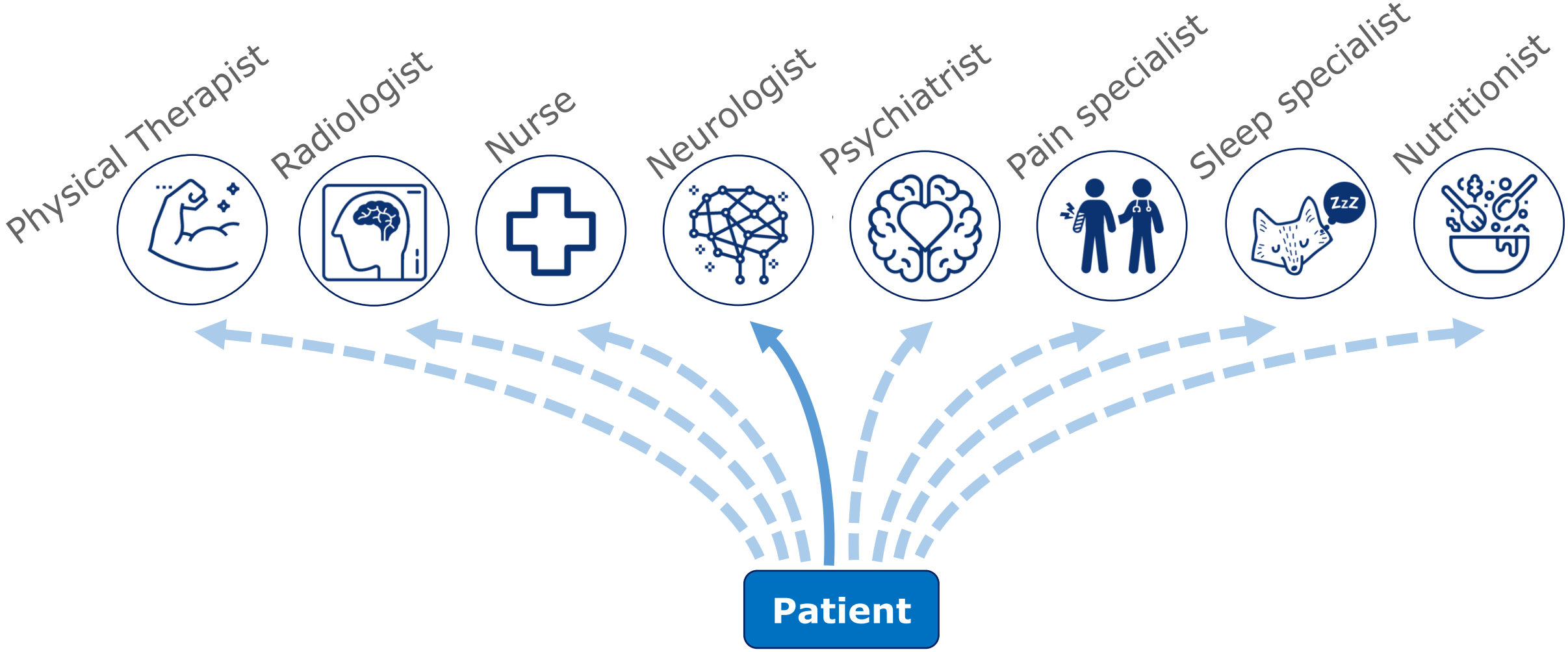
Silberstein et al. Neurology 2012;78:1337-45

Level U. Medications with conflicting evidence

- AEDs: gabapentin
- Antidepressants
  - SSRI/SNRIs: fluoxetine, fluvoxamine
  - Tricyclics: protriptyline
- Anti-thrombotics: acenocoumarol, Coumadin, picotamide
- β-Blockers: bisoprolol
- Calcium-channel blockers: nicardipine, nifedipine, nimodipine, verapamil
- Acetazolamide
- Cyclandelate

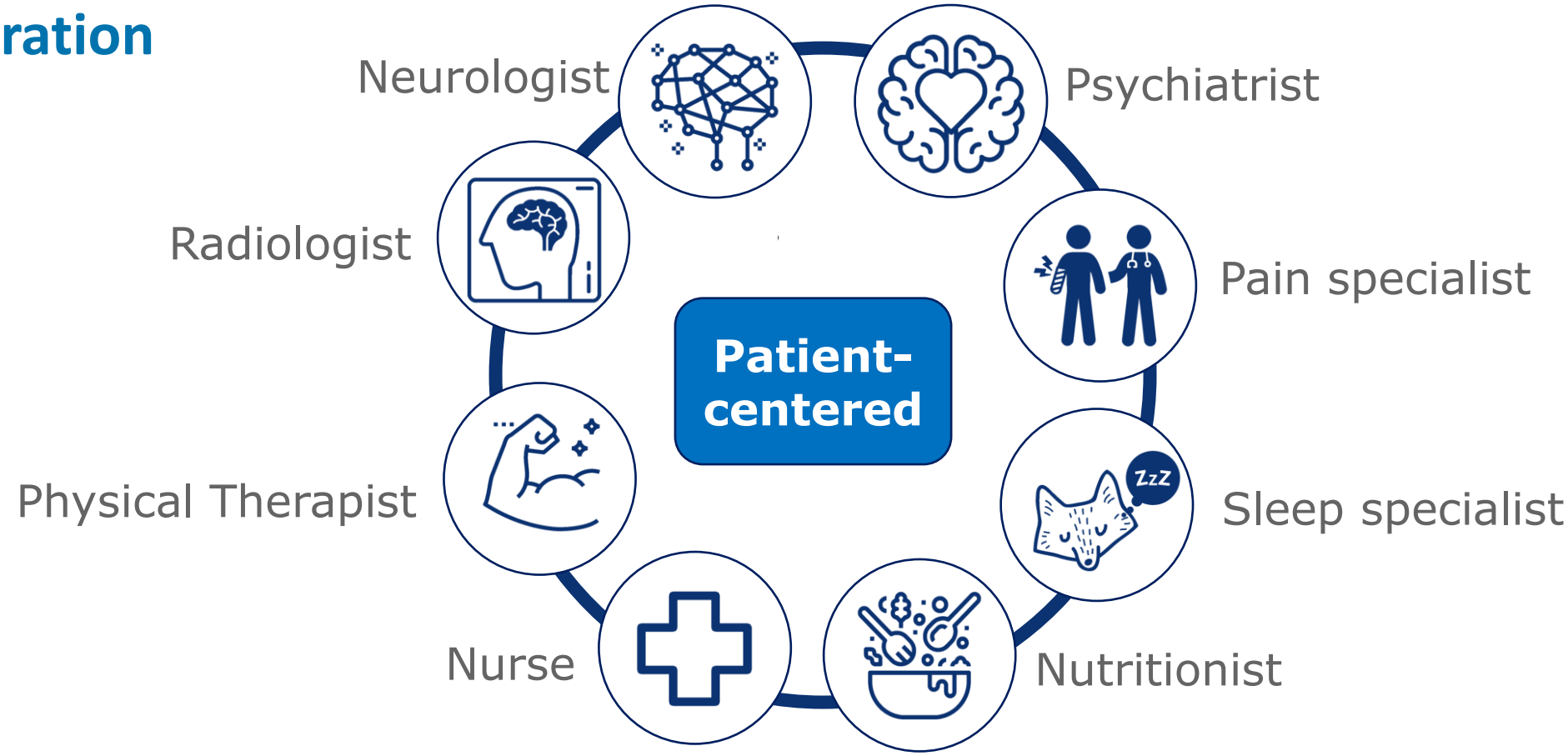
Silberstein et al. Neurology 2012;78:1337-45

Achieve 360° care for migraine



Achieve 360° care for migraine

- **Multidisciplinary teamwork**
- **Integration**



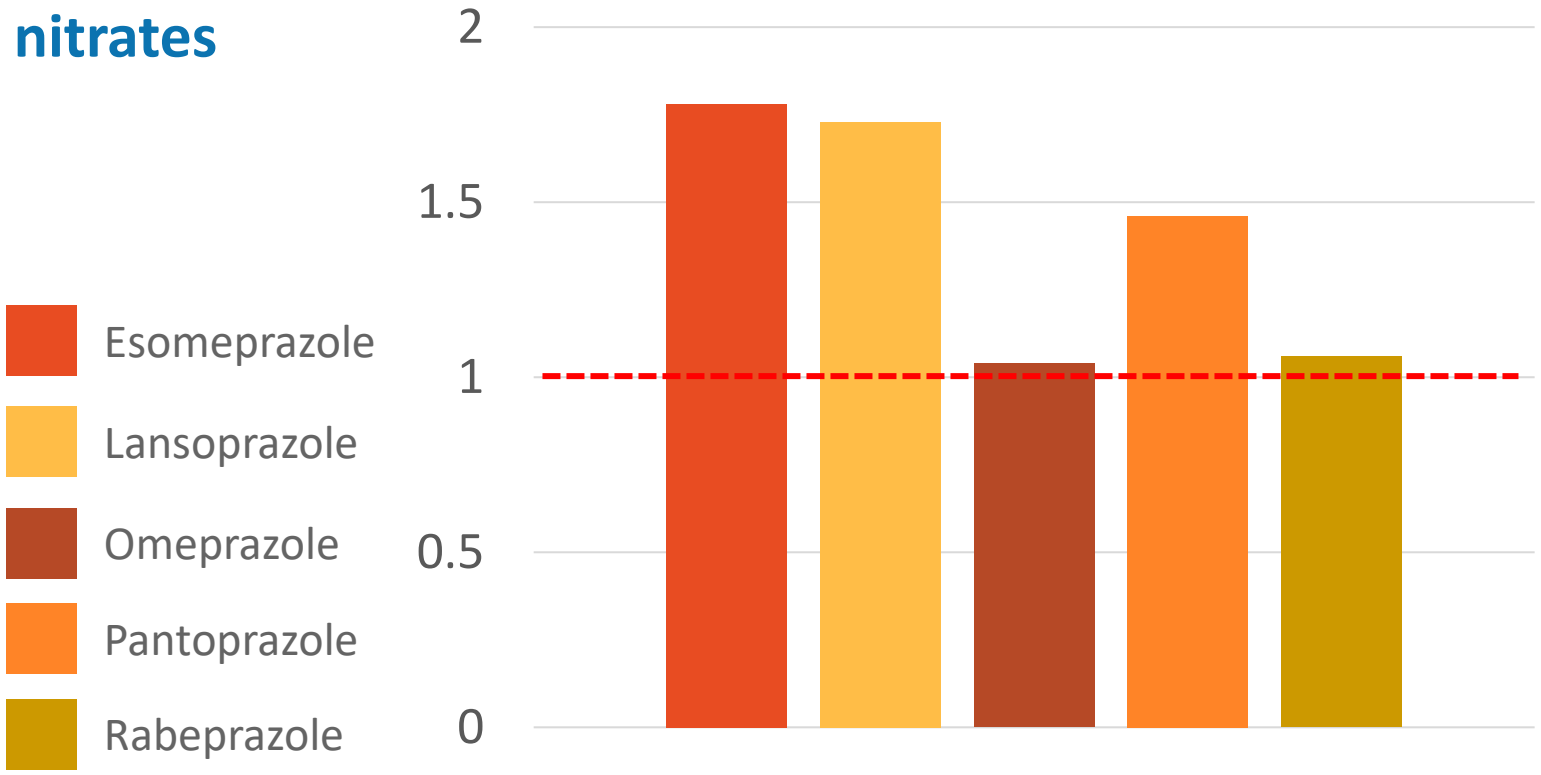
Clinical picture (continued):

- **Acute headache exacerbation for 1 month**

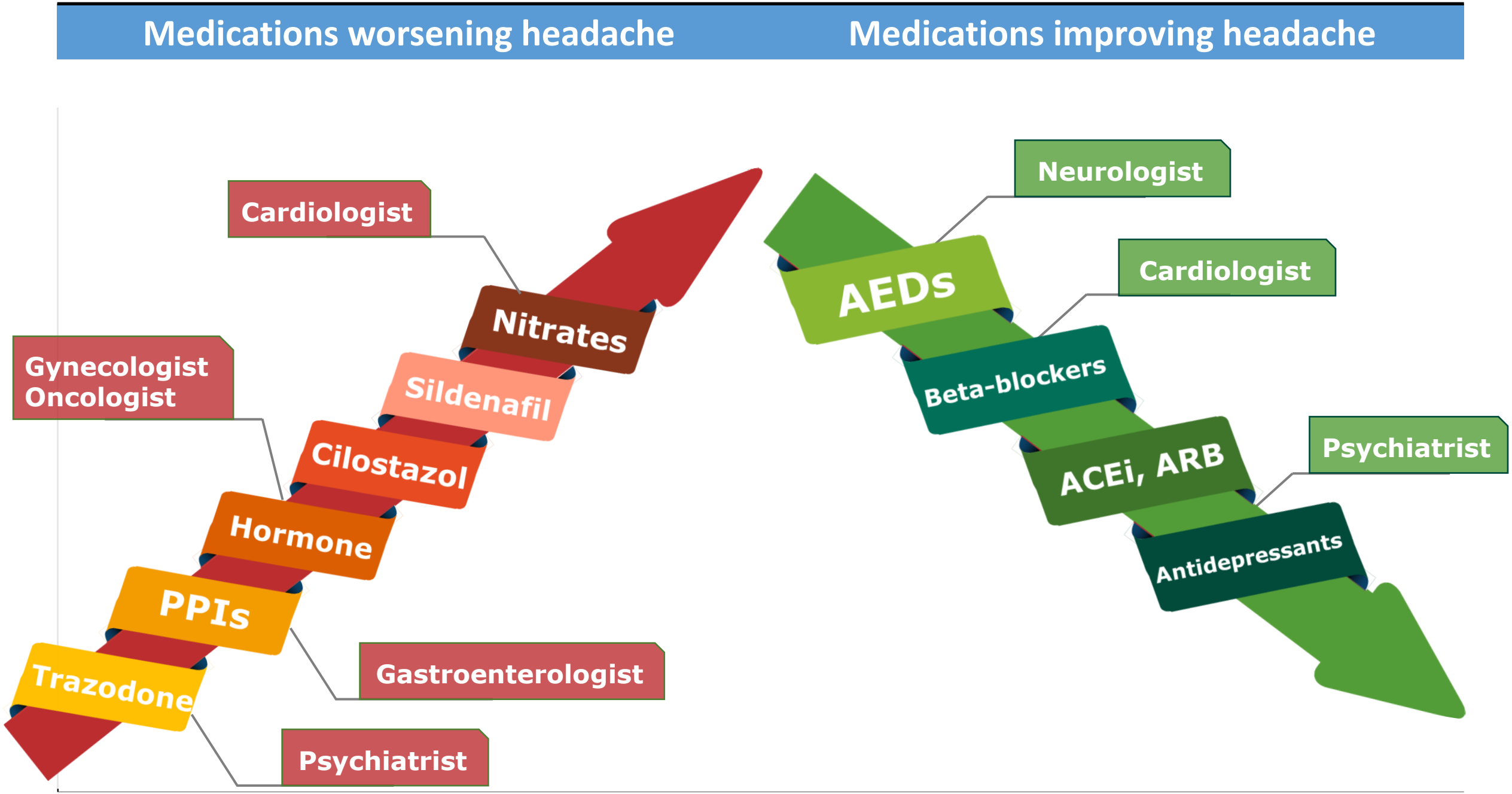
- Recent history:
  - Visited a gastroenterologist for GI upset
  - Prescribed esomeprazole (proton pump inhibitor)
  - Relevance?

Proton Pump Inhibitors (PPIs)

- Increases **1.8X** risk of headache within 7 days
  - Esp. **lansoprozole** & **esomeprazole**
  - Similar to **nitrates**



Liang, et al., Cephalalgia, 2014.


Medications worsening headache
Medications improving headache
Cardiologist
Nitrates
Gynecologist
Oncologist
Sildenafil
Cilostazol
Hormone
PPIs
Trazodone
Gastroenterologist
Psychiatrist
Neurologist
AEDs
Cardiologist
Beta-blockers
ACEi, ARB
Psychiatrist
Antidepressants

Take home messages (1)

- **Comorbidities** have a great **impact** on migraine patients
- Patients with primary headache disorders are suggested to be screened for psychiatric co-morbidity.
- Verbal screening may be adequate on a primary care level.
- Systematic and comprehensive screening should be performed at a referral center.
- Anxiety is as important as depression for headache patients.

Take home message (2)

- Severe or frequent headache → more psychiatric comorbidities and suicide attempts
- MA (vs. MO) → a stronger association with
  - Psychiatric disorders
  - Suicide risk
- Underlying mechanisms for comorbidity are not yet known.
- Anti-depressants can be considered to treat both migraine and psychiatric disorders
- Avoid migraine medications that may worsen comorbidities.

Take home messages (3)

- Build a “well-connected” **multidisciplinary team** to provide 360° care

- **Patient-centered** care to achieve better outcomes

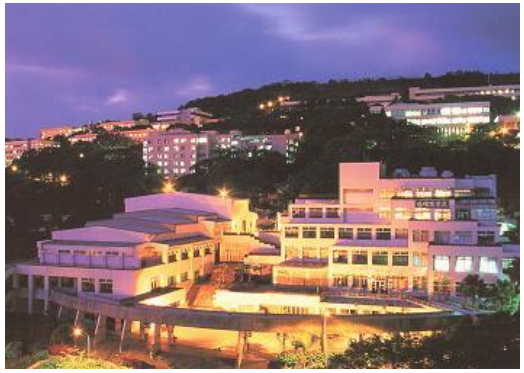
Since 2005
台灣頭痛學會
Taiwan Headache Society

Thanks for your attention!

王署君 Shuu-Jiun Wang, MD

sjwang@vghtpe.gov.tw

陽明交大
NYCU



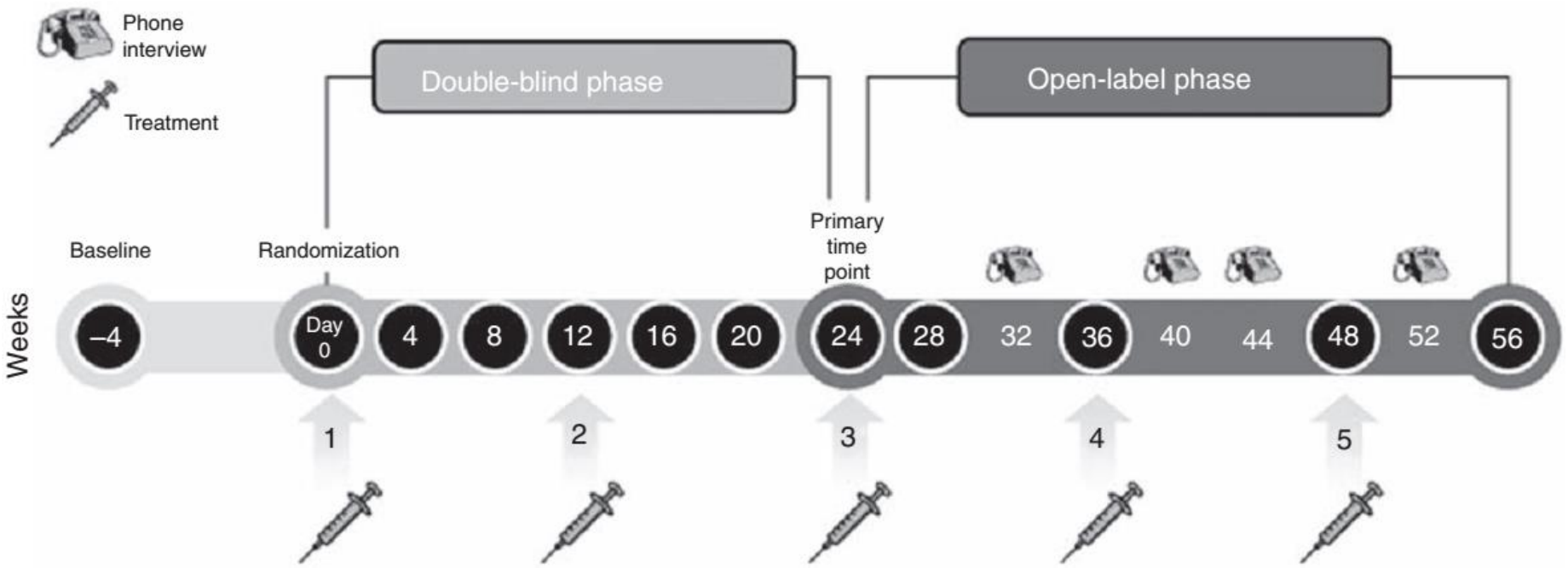
OnabotulinumtoxinA in the treatment of chronic migraine

Yen-Feng Wang
Department of Neurology
Taipei Veterans General Hospital
National Yang-Ming University

Apr. 11, 2021

PREEMPT 1 & 2

- The Phase III REsearch Evaluating Migraine Prophylaxis Therapy 1 & 2



Cephalalgia 2010; 30: 793-803.

PREEMPT baseline demographics and characteristics

	OnabotA (n = 688)	Placebo (n = 696)	p
Mean age, years	41.1	41.5	0.579
Female (%)	87.6	85.2	0.185
Caucasian (%)	89.7	90.5	0.602
Mean frequency of headache days	19.9	19.8	0.498
Mean frequency of migraine days	19.1	18.9	0.328
Mean frequency of moderate/severe headache days	18.1	18.0	0.705
Mean frequency of total cumulative hours of headache occurring on headache days	295.9	281.2	0.021
Patients with severe (≥ 60) HIT-6 score (%)	93.5	92.7	0.565

HIT, Headache Impact Test.

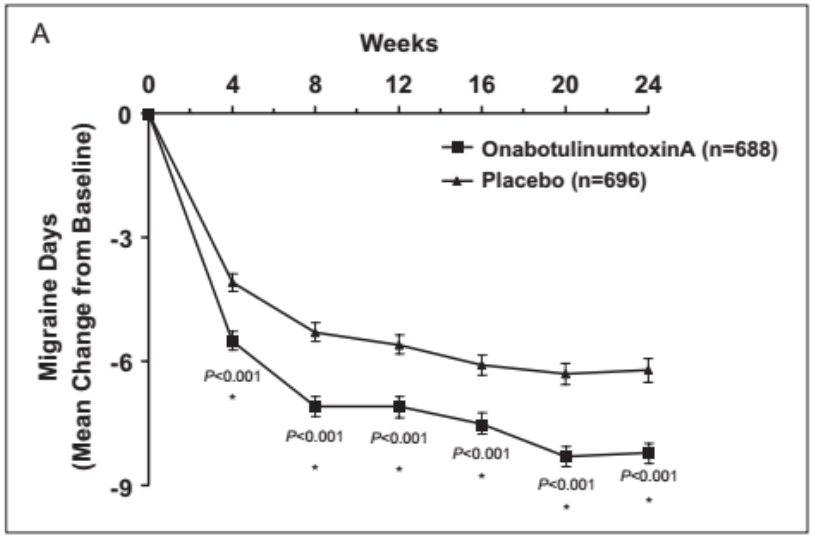
Adapted from Headache 2011;51:1358–73.

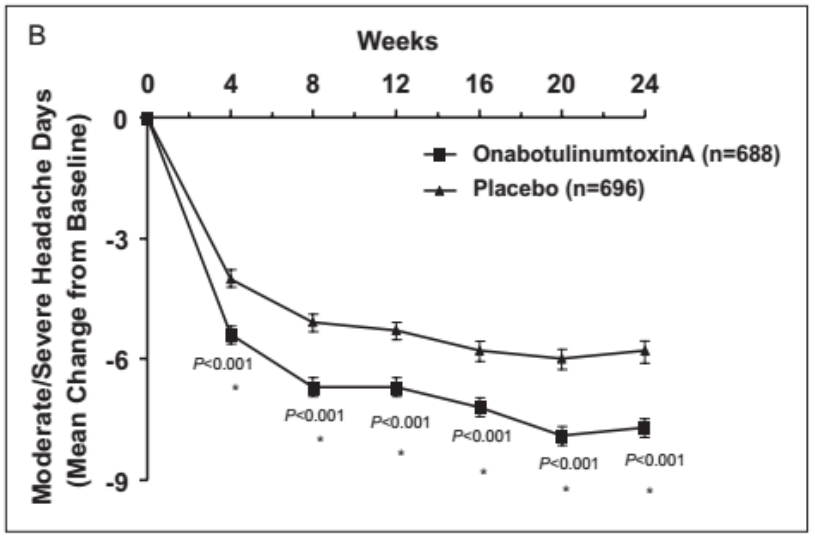
PREEMPT 1 & 2

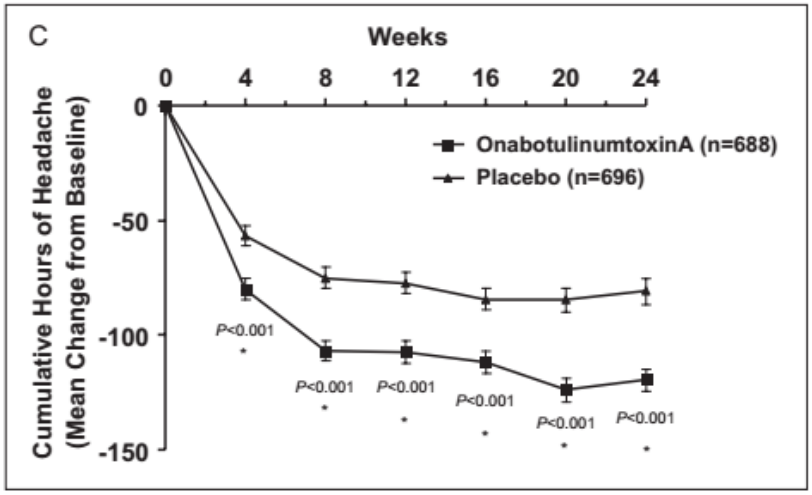
- PREEMPT 1: no decrease in headache episodes. Decreased headache days ($p=0.006$) and migraine days ($p=0.002$).
- PREEMPT 2: decreased headache episodes ($p=0.003$), headache days ($p<0.001$) and migraine days ($p<0.001$).
- Most frequent AEs: neck pain, muscle weakness.

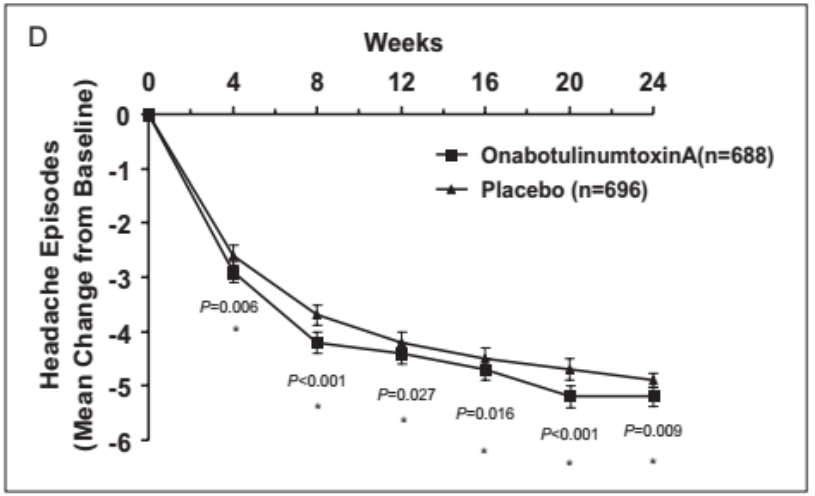
Cephalalgia 2010; 30: 793-803.
Cephalalgia 2010; 30: 804-814.

PREEMPT 1 & 2 pooled data



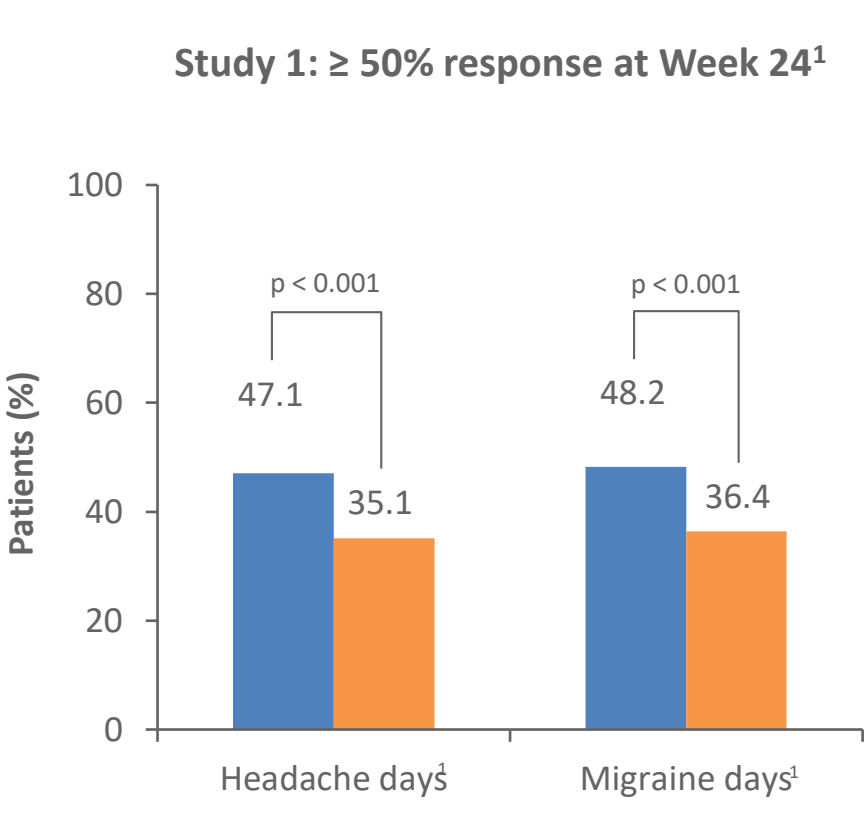


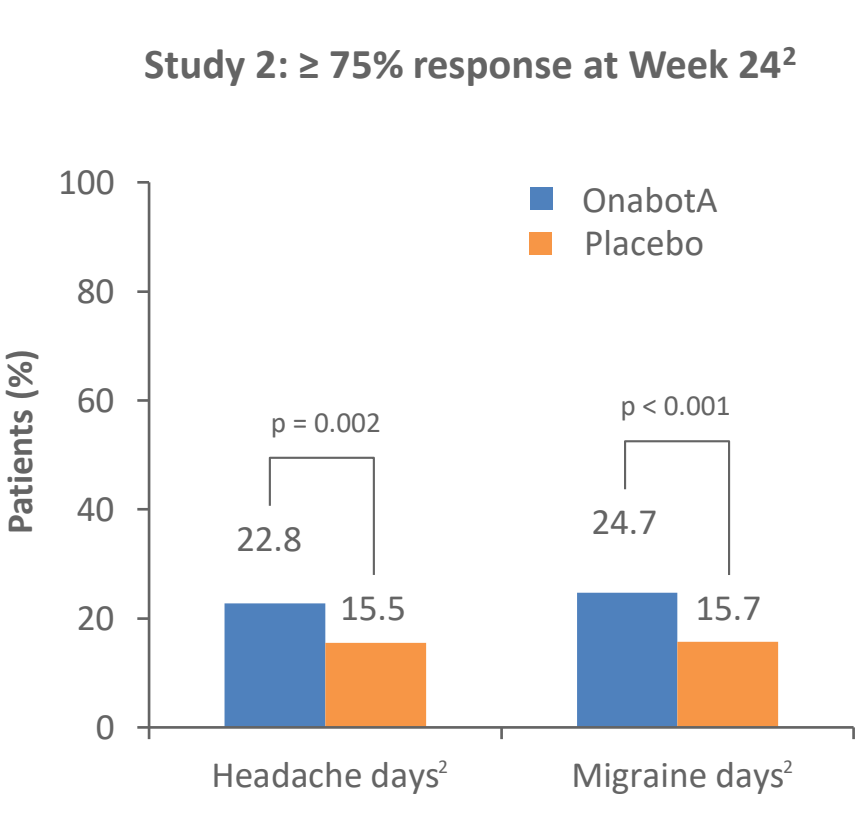




Headache 2010; 50: 921-936.

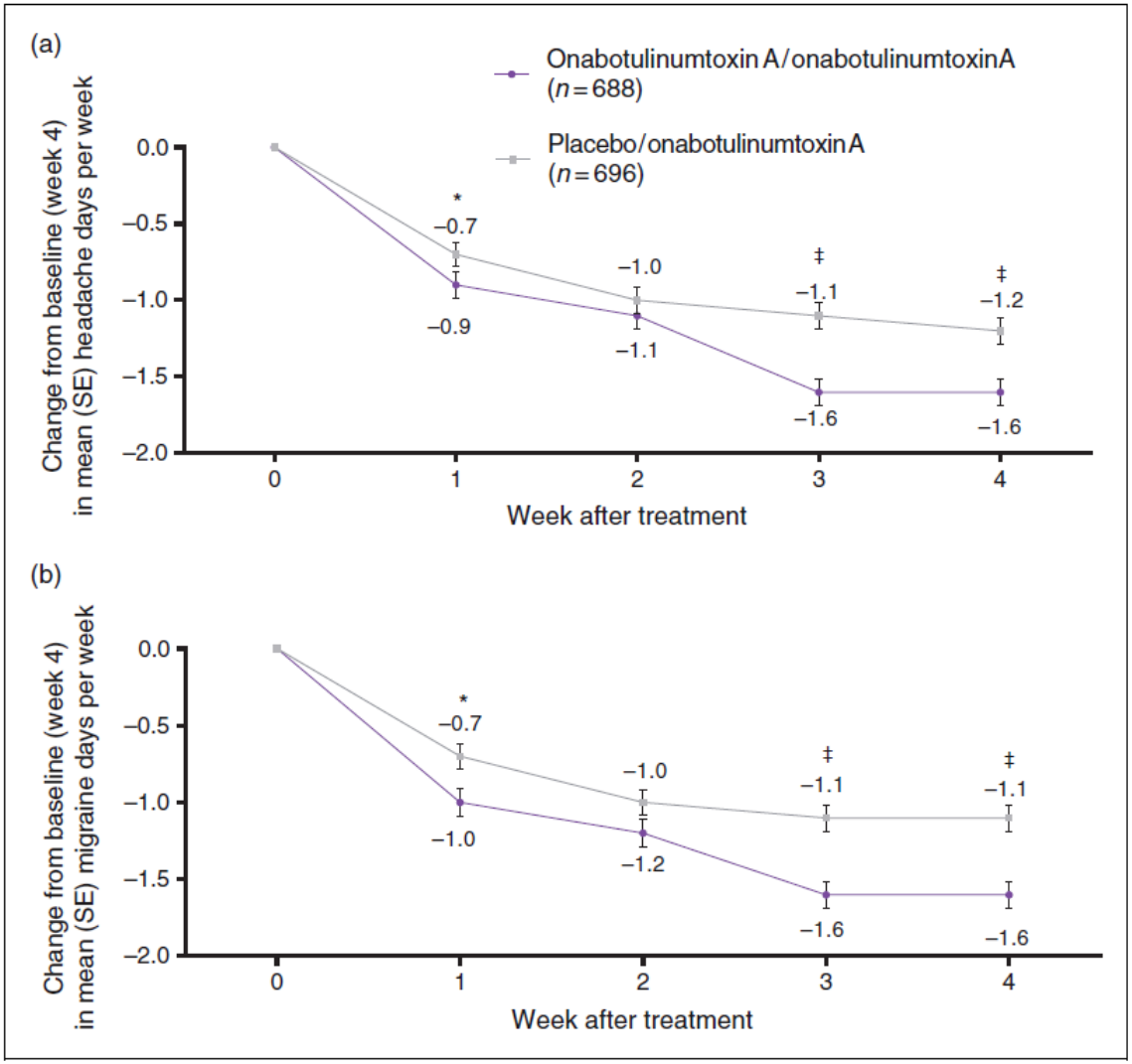
50% & 75% response rates at Week 24





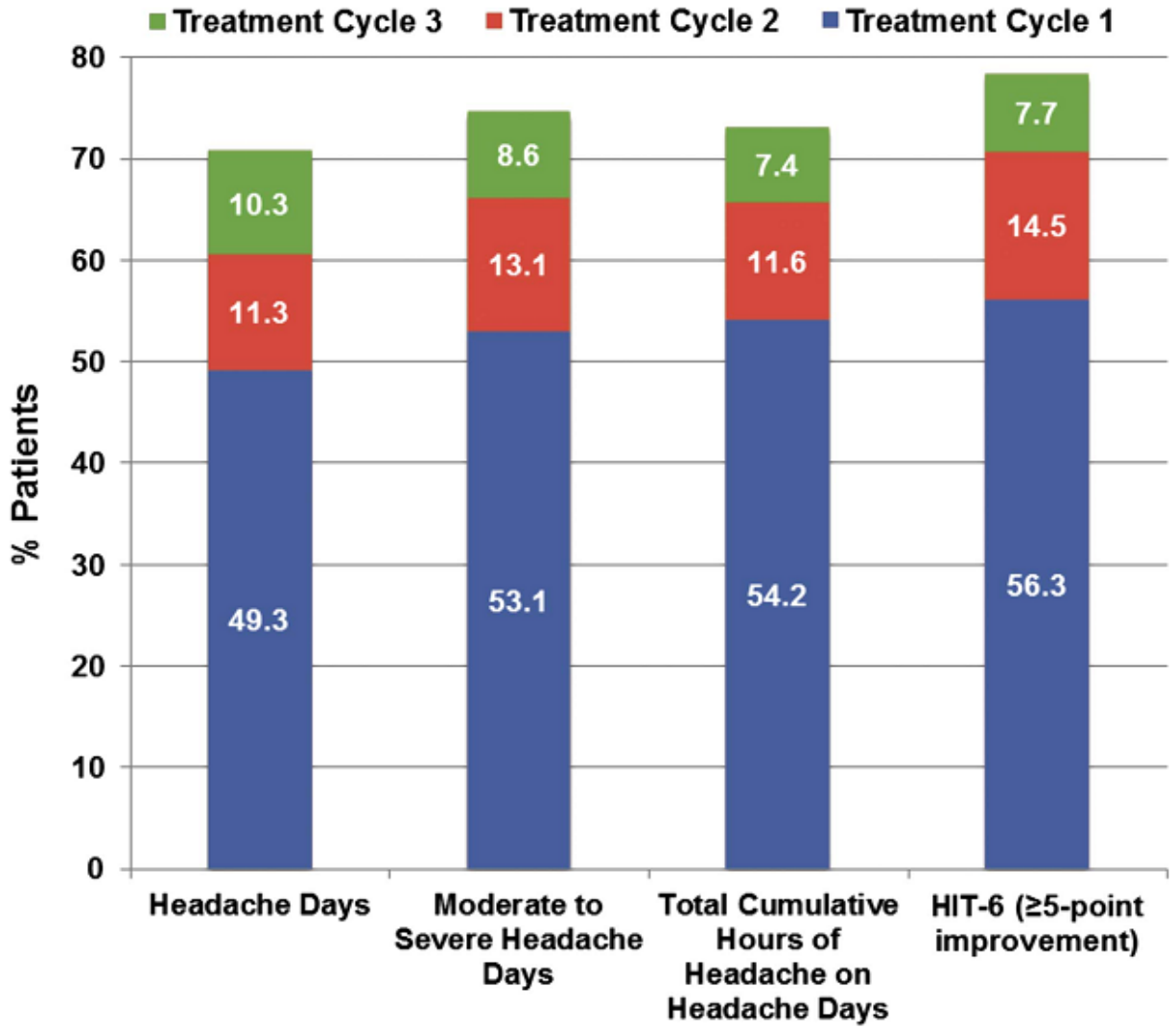
Adapted from 1. Aurora et al. Headache 2011;51:1358–73. 2. Dodick et al. Presented at the 15th Congress of IHS, 2011; Abstract PSI-I58.

How early does it start to work?



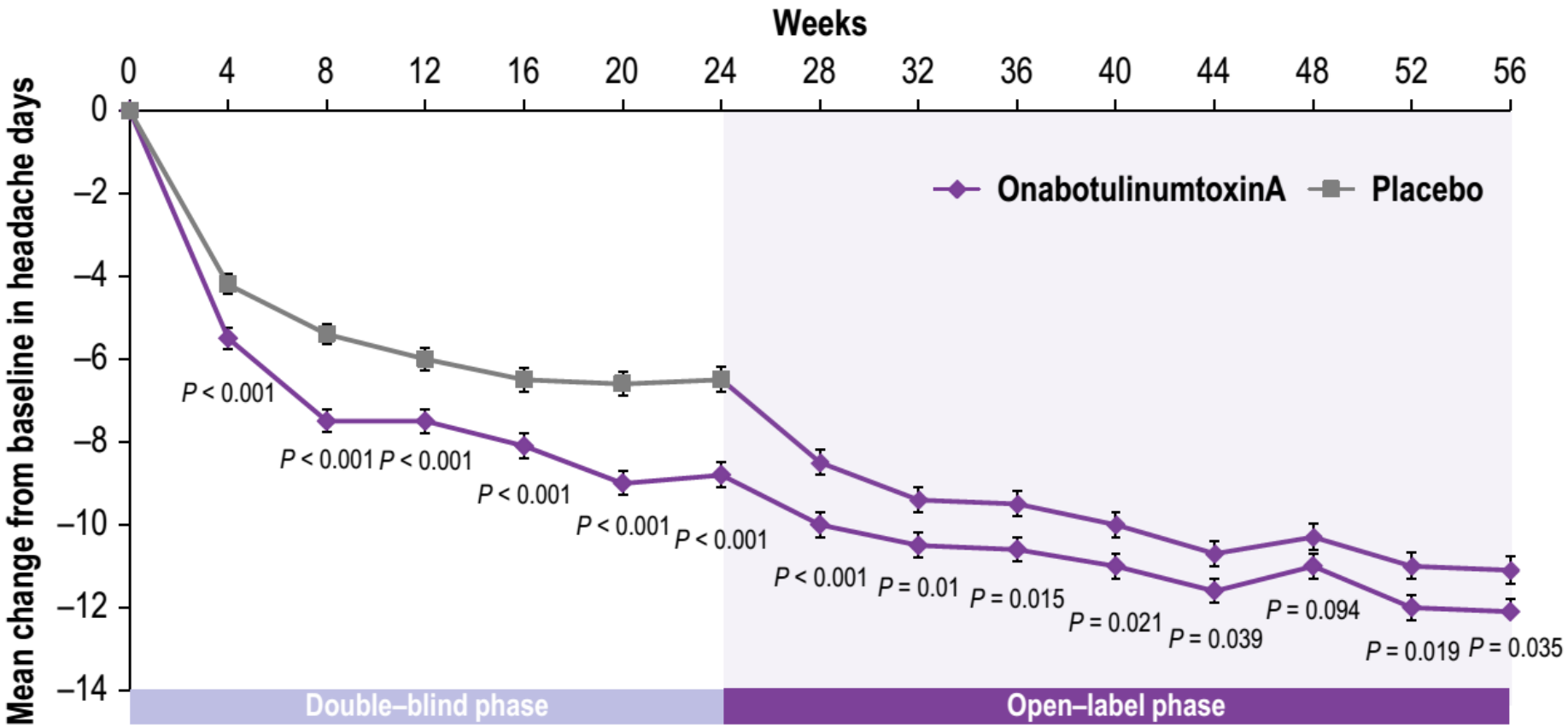
Cephalalgia. 2019; 39: 945-56.

Percentages of first-time 50% responders



J Neurol Neurosurg Psychiatry. 2015; 86: 996-1001.

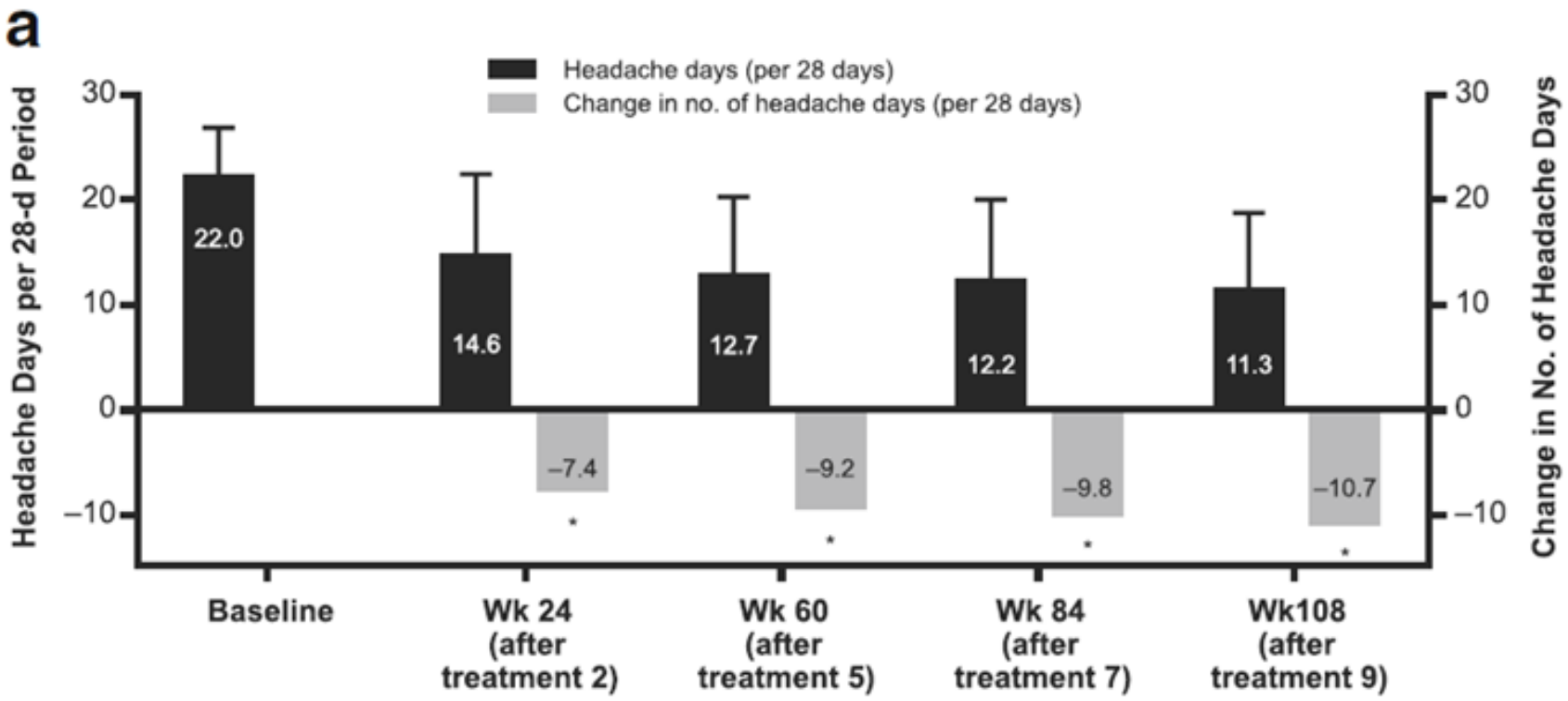
Long-term efficacy of BoTN-A



Acta Neurol Scand 2014: 129: 61–70

COMPEL study (RWD)

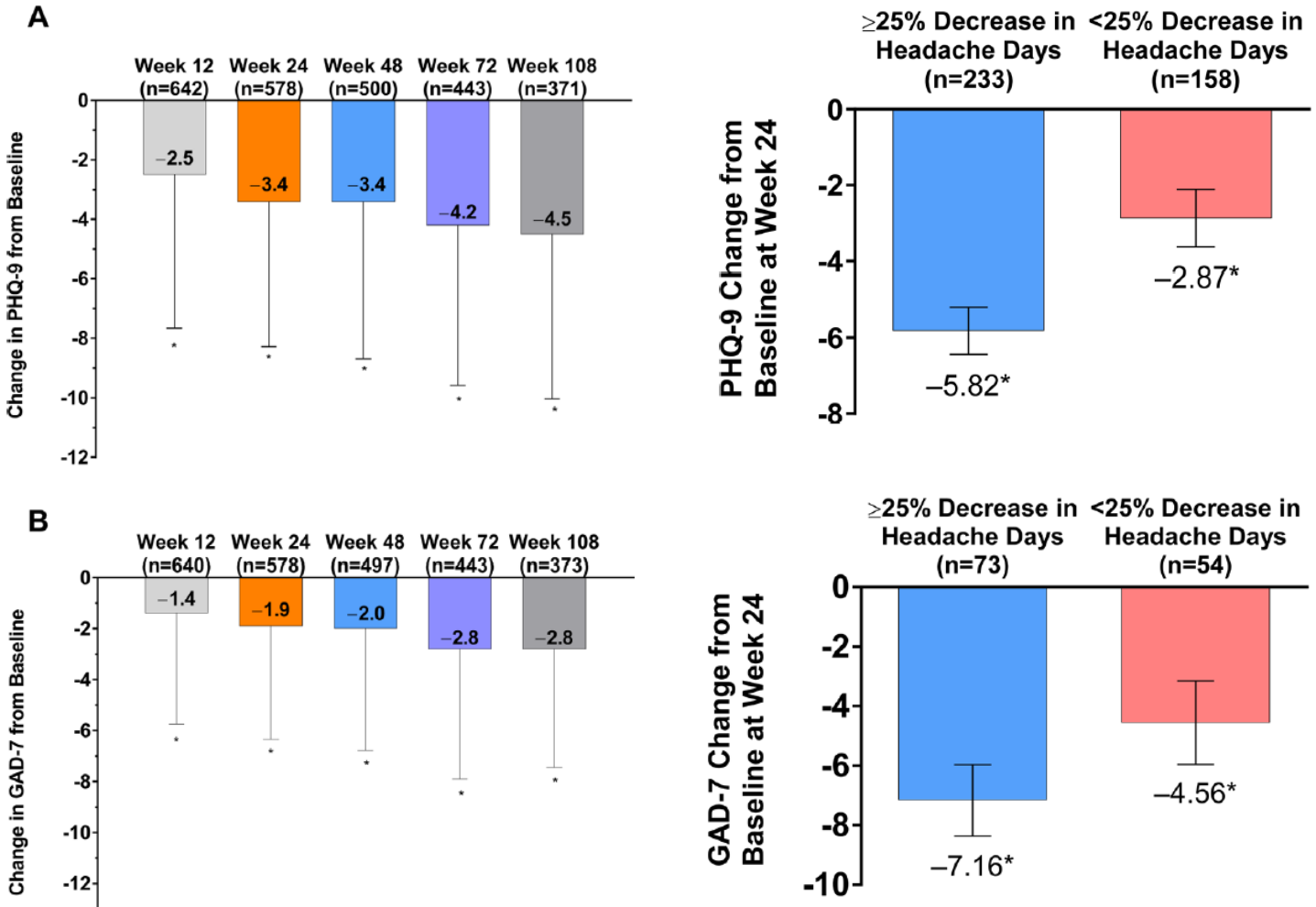
- 155U Q12W for 108 wks (US, KR, AU), n=716



J Headache Pain 2018; 19: 13.

Improvement in anxiety and depression

PHQ-9

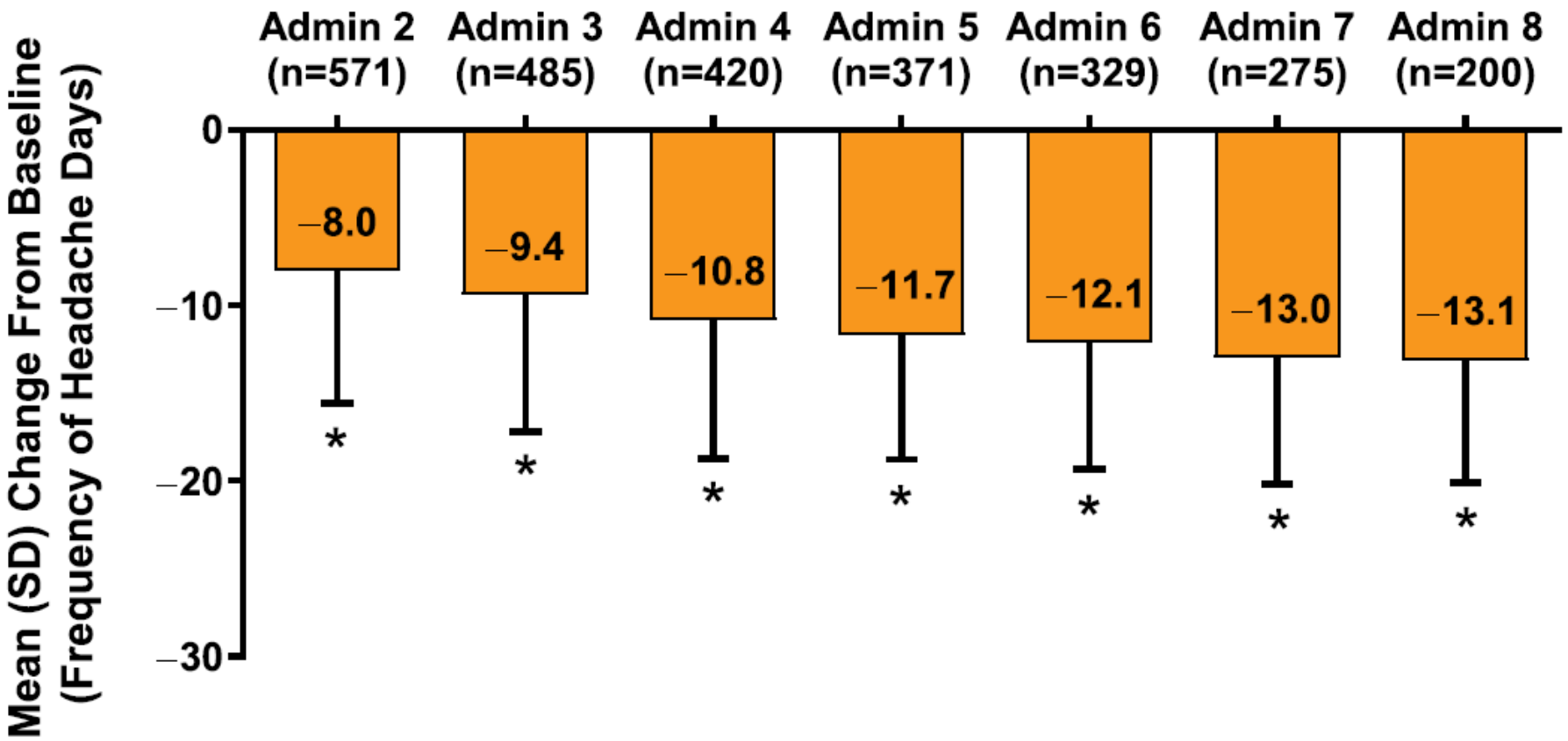


GAD-7

J Neurol Neurosurg Psychiatry 2019; 90: 353–360.

REPOSE study (RWD)

- 155-195U Q12W for 24M (EU), n=641



J Headache Pain 2019; 20: 26

Are CGRP mAbs more potent in CM?

ΔMHD

	Verum	Placebo
Erenumab	-6.6 (70/140)	-4.2
Eptinezumab	-7.7 (100)/-8.2 (300)	-5.6
Galcanezumab	-4.83 (120)/-4.62 (240)	-2.74
Fremanezumab	-4.6 (225M)/-4.3 (675Q)	-2.5

50%RR

	Verum	Placebo
Erenumab	40% (70)/41% (140)	23%
Eptinezumab	58% (100)/61% (300)	39%
Galcanezumab	27.6% (120)/27.5% (240)	15.4%
Fremanezumab	41% (225M)/38% (675Q)	18%

PREEMPT 1 & 2 DB phase

	OnabotulinumtoxinA (n = 687) n (%)	Placebo (n = 692) n (%)
All adverse events	429 (62.4)	358 (51.7)
Treatment-related adverse events	202 (29.4)	88 (12.7)
Serious adverse events	33 (4.8)	16 (2.3)
Treatment-related, serious adverse events	1 (0.1)	0 (0.0)
Discontinuations related to adverse events†	26 (3.8)	8 (1.2)
Death	0 (0.0)	0 (0.0)

- Neck pain (6.7%)
- Muscular weakness (5.5%)
- Ptosis (3.3%)
- Injection site pain (3.2%)

Headache 2010; 50: 921-936.

Adverse effects

	PREEMPT 1 & 2 DB		PREEMPT 1 & 2 OLE	COMPEL	REPOSE	CM PASS
	Onabot-A (n=687)	PCB (n=692)	(n=1205)	(n=716)	(n=633)	(n=1160)
TRAE	29.4%	12.7%	20.3%	18.3%	18.3%	25.1%
Neck pain	6.7%	2.2%	4.6%	4.1%	2.8%	4.4%
Eyelid ptosis	3.3%	0.3%	2.5%	2.5%	5.4%	4.1%
Musculoskeletal stiffness	2.3%	0.7%	1.7%	2.4%	2.7%	2.0%
Muscular weakness	5.5%	0.3%	3.9%	1.4%	n/a	2.7%
Injection-site pain	3.2%	2.0%	2.0%	2.0%	n/a	n/a
Headache	2.9%	1.6%	1.4%	1.7%	n/a	2.2%
Facial paresis	2.2%*	n/a	1.2%*	1.3%	n/a	1.3%

*Included in muscular weakness in PREEMPT 1 & 2 studies

VGH experience

Table 4
Adverse events according to botulinum toxin type A injection dosage.

	155 U $n = 27$	100 U $n = 59$	75 U $n = 8$	Total $n = 94$
All adverse effects	9 (33.3)	17 (28.8)	1 (12.5)	27 (28.7)
Lateral eyebrow elevation	7 (25.9)	11 (18.6)	0 (0)	18 (19.1)
Neck soreness	2 (7.4)	3 (5.1)	0 (0)	5 (5.3)
Ptosis	0 (0)	3 (5.1)	1 (12.5)	4 (4.3)

Data are presented as *n* (%).

J Chin Med Assoc 2014; 77: 10-15.

Guidelines

- AAN guideline
- EHF guideline
- NICE guidance
- THS guideline
- NHI reimbursement regulation

AAN guidelines on OnabotA

- CM: should be offered

  - increase the No. of HA-free days (level A)

  - reduce HA impact on HRQoL (level B)

- EM: should NOT be offered (level A)
- CTTH: probably ineffective (two Class I studies) (Level B, as determined in 2008 guideline).

AMERICAN ACADEMY OF NEUROLOGY®

Neurology 2016; 86: 1818–1826.

EHF guidelines & NICE guidance

	EHF	NICE
Indication	CM	CM
Time to initiate	Failed 2-3 preventives	Failed ≥ 3 preventives
MOH	Withdrawal before initiation of OnabotA	Appropriately managed
Time to stop	1. No response after 2-3 tx cycles (< 30% reduction) 2. Reduction to < 10 HA days/M for 3M (re-evaluated 4–5M after DC)	1. No response after 2 tx cycles (< 30% reduction) 2. Has changed to EM for 3 consecutive months

J Headache Pain 2018; 19: 91.

https://www.nice.org.uk/guidance/ta260

偏頭痛預防性藥物治療準則

黃子洲、賴資賢 暨台灣頭痛學會治療準則小組

中文摘要

本小組針對國內臨床使用的偏頭痛預防治療藥物，以實證醫學的方式，評估新發表之藥物試驗研究，整合原有資訊，並參考歐美最新的治療準則，經由小組會議討論辯證，對藥物使用於偏頭痛預防治療之主要角色，推薦等級，藥物不良反應及使用注意事項提出共識，並更新之前於2008 年出版之準則。

臺灣目前可用於陣發性偏頭痛預防性發作治療之藥物可分爲乙型阻斷劑、抗癲癇藥物、鈣離子阻斷劑、抗憂鬱劑、非類固醇抗發炎藥物、肉毒桿菌素與其他藥物。其中，propranolol 證據等級最佳，且副作用相對少，建議做第一線治療。Valproic acid、topiramate、flunarizine 和 amitriptyline 建議爲第二線治療。其他類藥物建議於上述藥物無效後使用。慢性偏頭痛則建議肉毒桿菌素注射或是 topiramate，其次才是用於預防陣發性偏頭痛的建議用藥。懷孕及哺乳婦女非必要不建議使用偏頭痛預防性藥物。月經偏頭痛可使用非類固醇類抗發炎製劑或是翠普登類藥物於月經期作爲預防治療。兒童、青少年及老年人的偏頭痛預防藥物臨床證據尚不足。

預防用藥必須由小劑量開始，並逐漸增至有效劑量，減少不良反應及提高耐受性。預防偏頭痛藥物一般需使用 3 到 4 週才能評估療效，治療需持續 6 個月，待頭痛減少後，逐漸減藥與停藥。除使用預防用藥外，應同時注意病人是否有過度使用急性治療藥物。

Since 2005 台灣頭痛學會 Taiwan Headache Society

Acta Neurol Taiwan 2017;26:33-53.

台灣健保給付規定-1

(1)需經事前審查核准後使用。

(2)限神經內科或神經外科專科醫師診斷及注射。

(3)需符合慢性偏頭痛診斷：至少有3個月時間，每個月≧15天，每次持續4小時以上，且其中符合偏頭痛診斷的發作每個月≧8天。(重要限制：Botox對每個月頭痛天數≤14天的陣發性偏頭痛之安全性及有效性，尚無證據證實其療效)。

台灣健保給付規定-2

(4)患者需經3種（含）以上偏頭痛預防用藥物（依據台灣頭痛學會發表之慢性偏頭痛預防性藥物治療準則之建議用藥，至少包括topiramate）治療無顯著療效，或無法忍受其副作用。

(5)每次注射最高劑量Botox 155單位，且每年最多4個療程。

(6)首次申請給付2個療程，2個療程治療之後，評估每月頭痛天數，需比治療前降低50%以上，方可持續給付。

台灣健保給付規定-3

(7)接續得申請一年療程，分為4次注射治療。療程完畢後半年內不得再次申請。

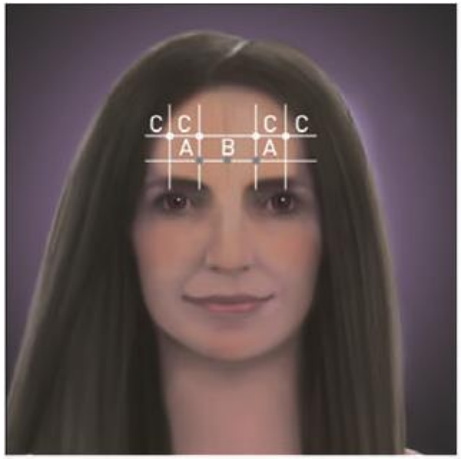
(8)若病況再度符合慢性偏頭痛診斷，得再次申請一年使用量時，需於病歷記錄治療後相關臨床資料，包括頭痛天數。

(9)神經內科、神經外科專科醫師需經台灣神經學學會訓練課程認證慢性偏頭痛診斷與Botox PREEMPT 155U 標準注射法。

PREEMPT protocol

- Corrugator
- Procerus
- Frontalis
- Temporalis
- Occipitalis
- Cervical paraspinals
- Trapezius

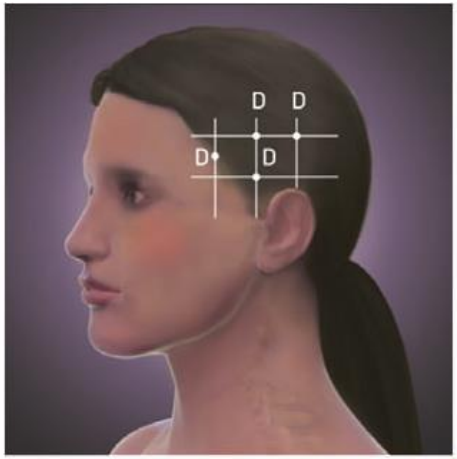
Fixed-site, fixed-dose injection site locations (155U)



A. Corrugator
5 U each side

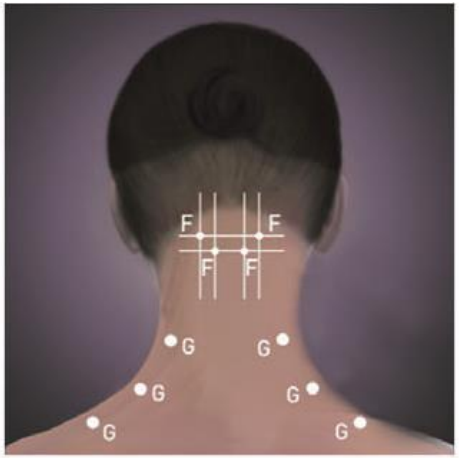
B. Procerus
5 U (one site)

C. Frontalis
10 U each side



D. Temporalis
20 U each side

E. Occipitalis
15 U each side



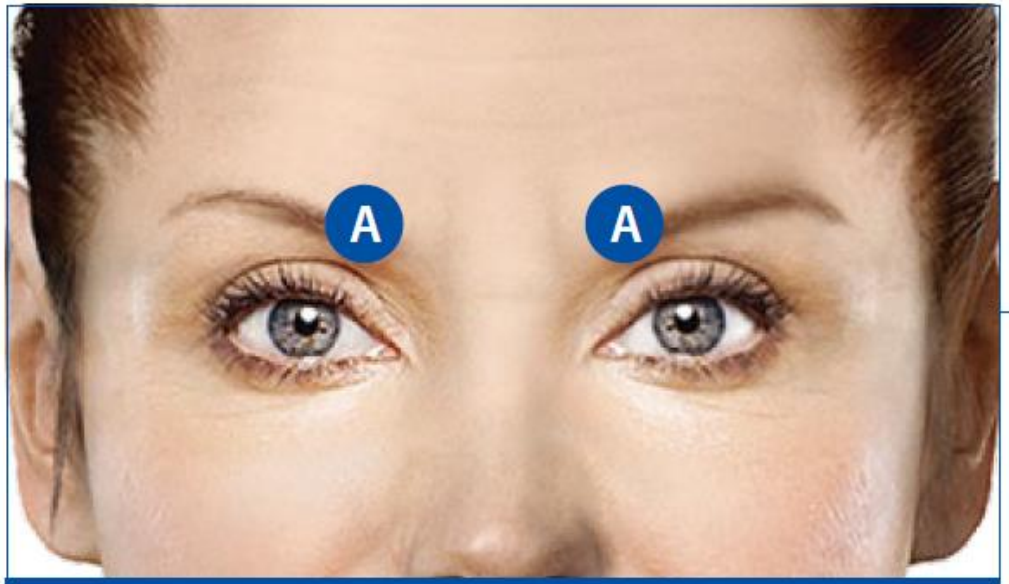
F. Cervical paraspinal
10 U each side

G. Trapezius
15 U each side

6-7-8-10


Ultra-Fine™ II
Short Needle • Insulin Syringe
BD Ultra-Fine™ II
Short Needle • Insulin Syringe
Use with U-100 Insulin
0,30mm (30G) x 8mm
Non-Toxic • Non-Pyrogenic
REF 326702
1mL
EN ISO 8537
STERILE R
0050
DO NOT REUSE
주 사 기
KOVAX-SYRINGE®
FOR SINGLE USE
1 mL
KOREA VACCINE CO., LTD.
STERILE EO
CE 0120
Non-Toxic
Non-Pyrogenic
PEEL OPEN
Sterility guaranteed unless package has been opened or damaged.
25GX 1"
LOT 0190514
190524
TUBERCULIN STERILE SINGLE USE
SINGLE USE ONLY
Webast

Corrugator (90°)



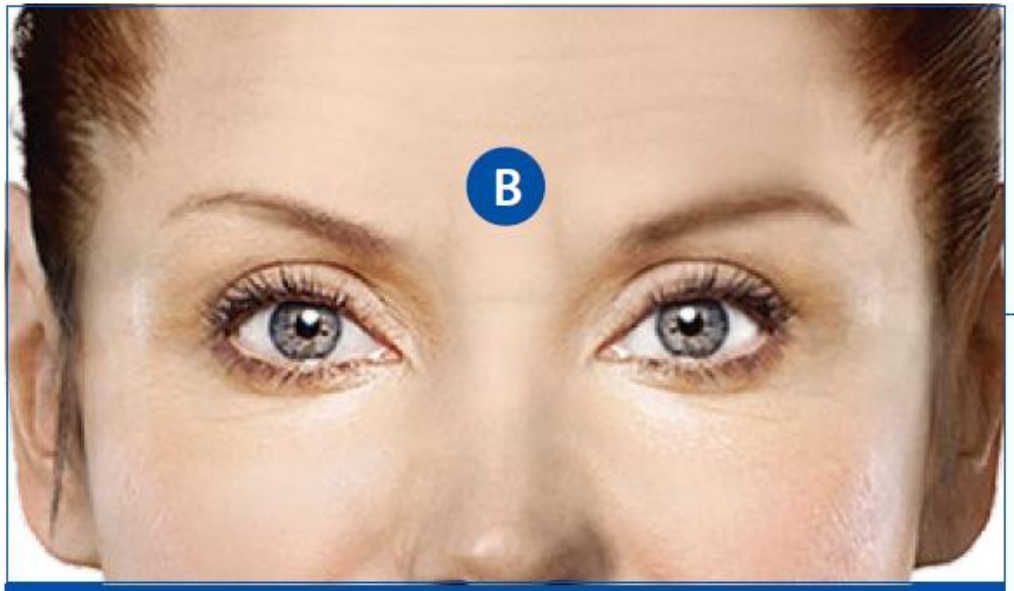
Corrugator injection sites[1]

A

Injection site[1]

- About 1.5 cm (1 fingerbreadth) above the medial inferior edge of the superior orbital rim (bony landmark). This may vary based on individual anatomy

Procerus (90º)



Procerus injection site[1]

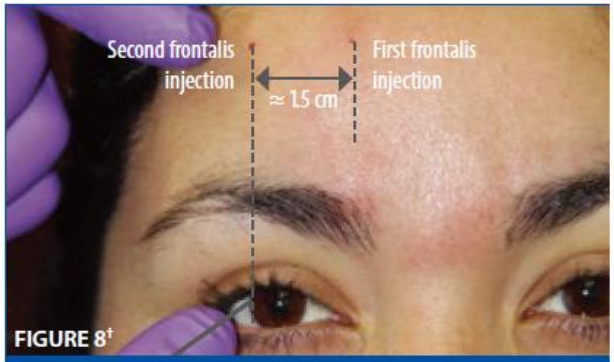
B

Injection site[1]

- The base of the procerus resides approximately midway between the 2 corrugator injections

Frontalis (45°)

Frontalis injection sites[1]



Lateral limbus of the cornea[18*]

C1

Medial injection site[1]

- Visually, draw a vertical line up from the medial inferior edge of the superior orbital rim
- Medial injection is generally within the upper one-third of the forehead, and at least 1.5 cm (~1 fingerbreadth) above the corrugator injection site. This may vary based on individual anatomy

C2

Lateral injection site[1]

- Lateral injections are parallel, lining up with the lateral limbus of the cornea, and at least 1.5 cm (~1 fingerbreadth) lateral to the medial injection site (Figure 8). This may vary based on individual anatomy

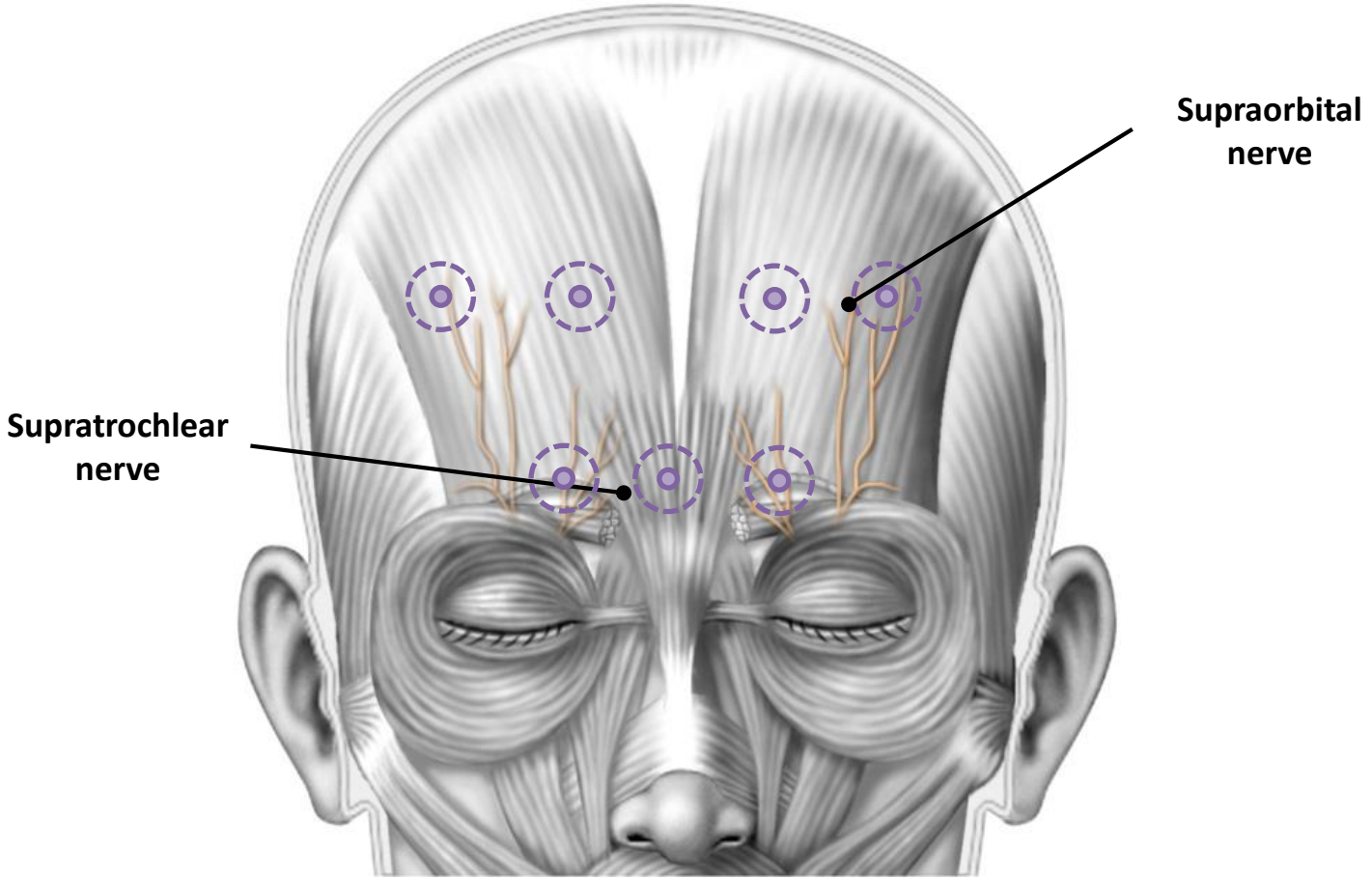


Image adapted from Binder & Blitzer 2003 and Blumenfeld 2010.

1. Binder & Blitzer. Facial Plast Surg Clin N Am 2003;11:465–75.
2. Blumenfeld et al. Headache 2010;**50**:1406–18.

Temporalis (45°)

D1

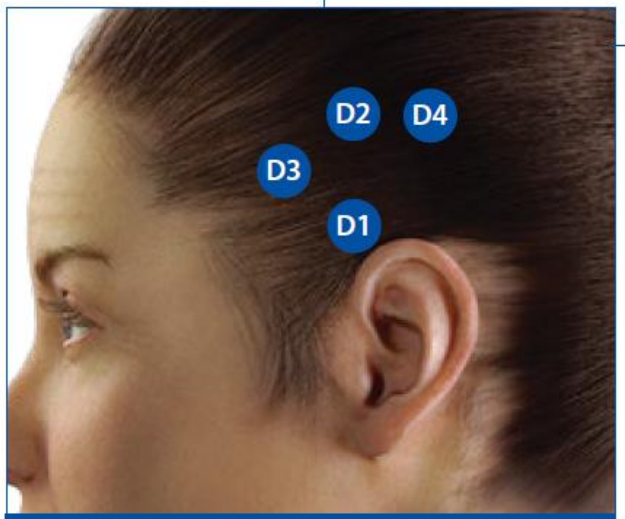
Injection site[1]

- Find the tragus of the ear and move your finger vertically up the side of the head about 3 cm (~2 fingerbreadths)

D2

Injection site[1]

- Move about 1.5 cm to 3 cm (~1-2 fingerbreadths) up from the first injection, still in line with the tragus of the ear



Temporalis injection sites[1]

D3

Injection site[1]

- Move about 1.5 cm (~1 fingerbreadth) forward, toward the face, from the first and second injections. Make the third injection halfway vertically between injection sites 1 and 2

D4

Injection site[1]

- Move about 1.5 cm (~1 fingerbreadth) back from the second injection, and in line with the midportion (helix) of the ear

*Muscles and anatomical structures shown for anatomical reference only.

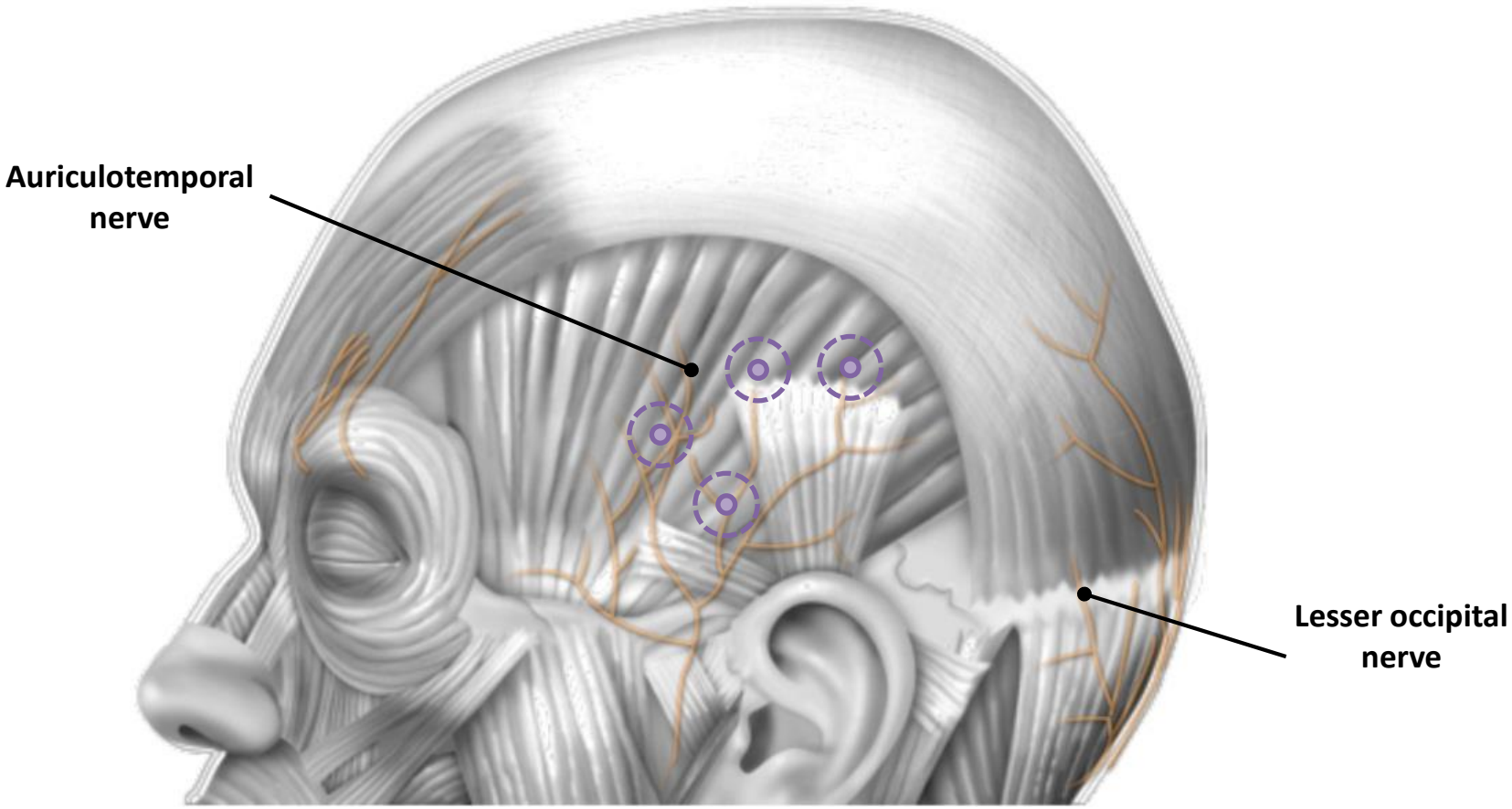
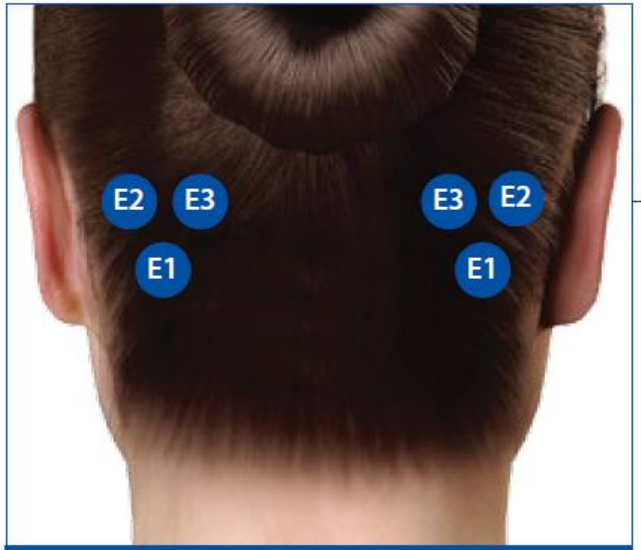


Image adapted from Binder & Blitzer 2003 and Blumenfeld 2010.

1. Binder & Blitzer. Facial Plast Surg Clin N Am. 2003;11:465–75.
2. Blumenfeld et al. Headache 2010;50:1406–18.

Occipitalis (45°)



Occipitalis injection sites[1]

*Muscles and anatomical structures shown for anatomical reference only.

E1

Injection site[1]

- Palpate the occipital protuberance and find the most posterior point (inion) in the midline (Figure 13, page 25)
- Locate the tip of the mastoid process behind the ear (Figure 13, page 25)
- Place the first injection just above the nuchal ridge at this midpoint

E2

Injection site[1]

- Measure a diagonal fingerbreadth up and out toward the superior helix of the ear (see diagram on page 20) for the second muscle area for injection (eg, at the 10 o'clock position for the left injection)

E3

Injection site[1]

- Measure a diagonal fingerbreadth up and medial for the third muscle area for injection (eg, at the 2 o'clock position for the left injection)

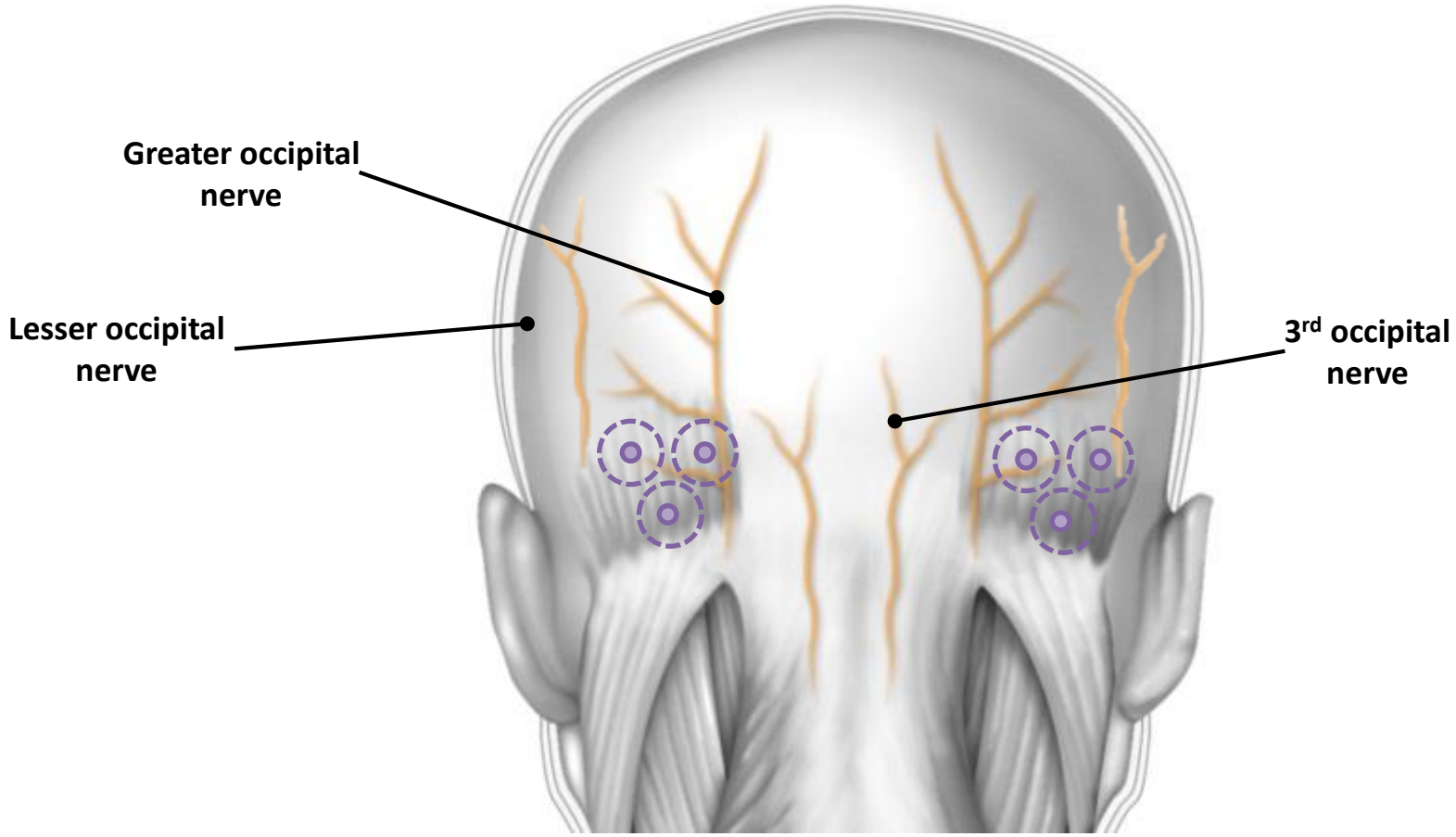
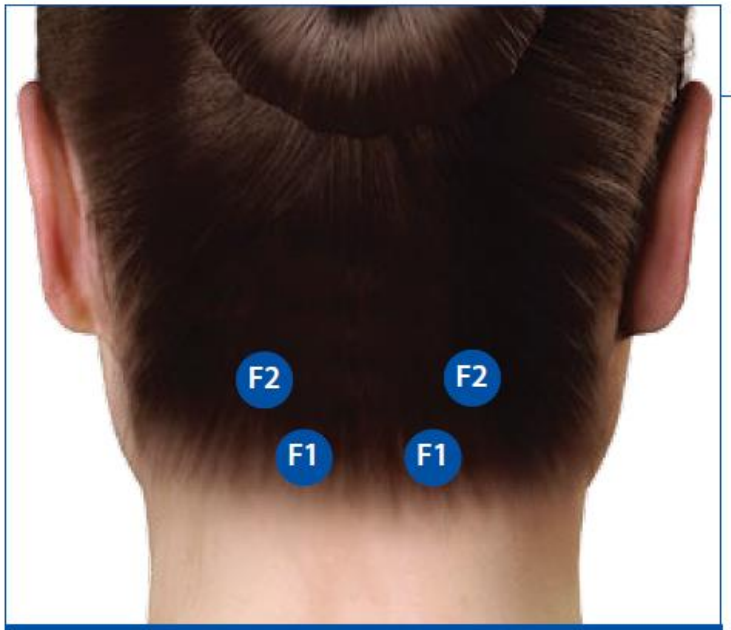


Image adapted from Binder & Blitzer 2003 and Blumenfeld 2010.

Adapted from: 1. Binder & Blitzer. Facial Plast Surg Clin N Am 2003;11:465–75. 2. Blumenfeld et al. Headache 2010;50:1406–18.

Cervical paraspinals (45°)



Cervical paraspinal injection sites[1]

F1

Injection site[1]

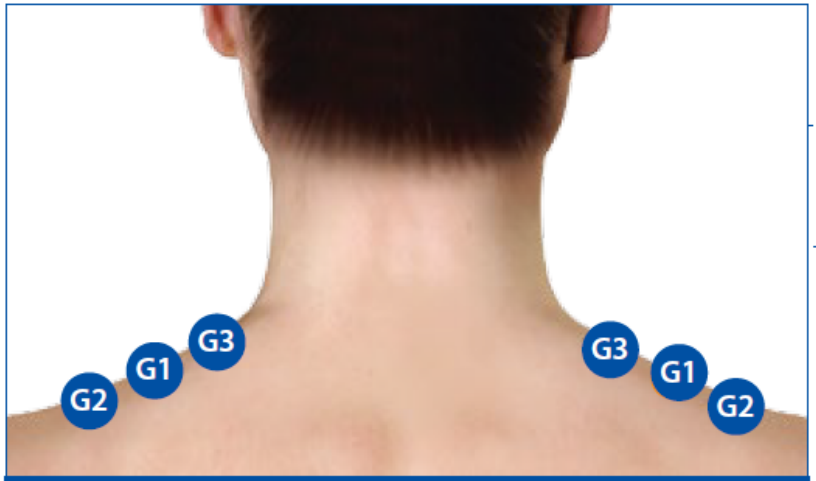
- Measure about 1 cm left of the midline of the cervical spine and about 3 cm (~2 fingerbreadths) inferior to the lower border of the occipital protuberance

F2

Injection site[1]

- Measure about 1.5 cm (~1 fingerbreadth) diagonally up at a 45° angle toward the helix of the ear (see diagram on page 20) from the first injection site

Trapezius (180º)



Trapezius injection sites[1]

G1

Injection site[1]

- Divide the upper portion of the trapezius muscle in half, from the inflection point of the neck (necklace line) to the acromioclavicular joint
- The first injection is located at this midpoint

G2

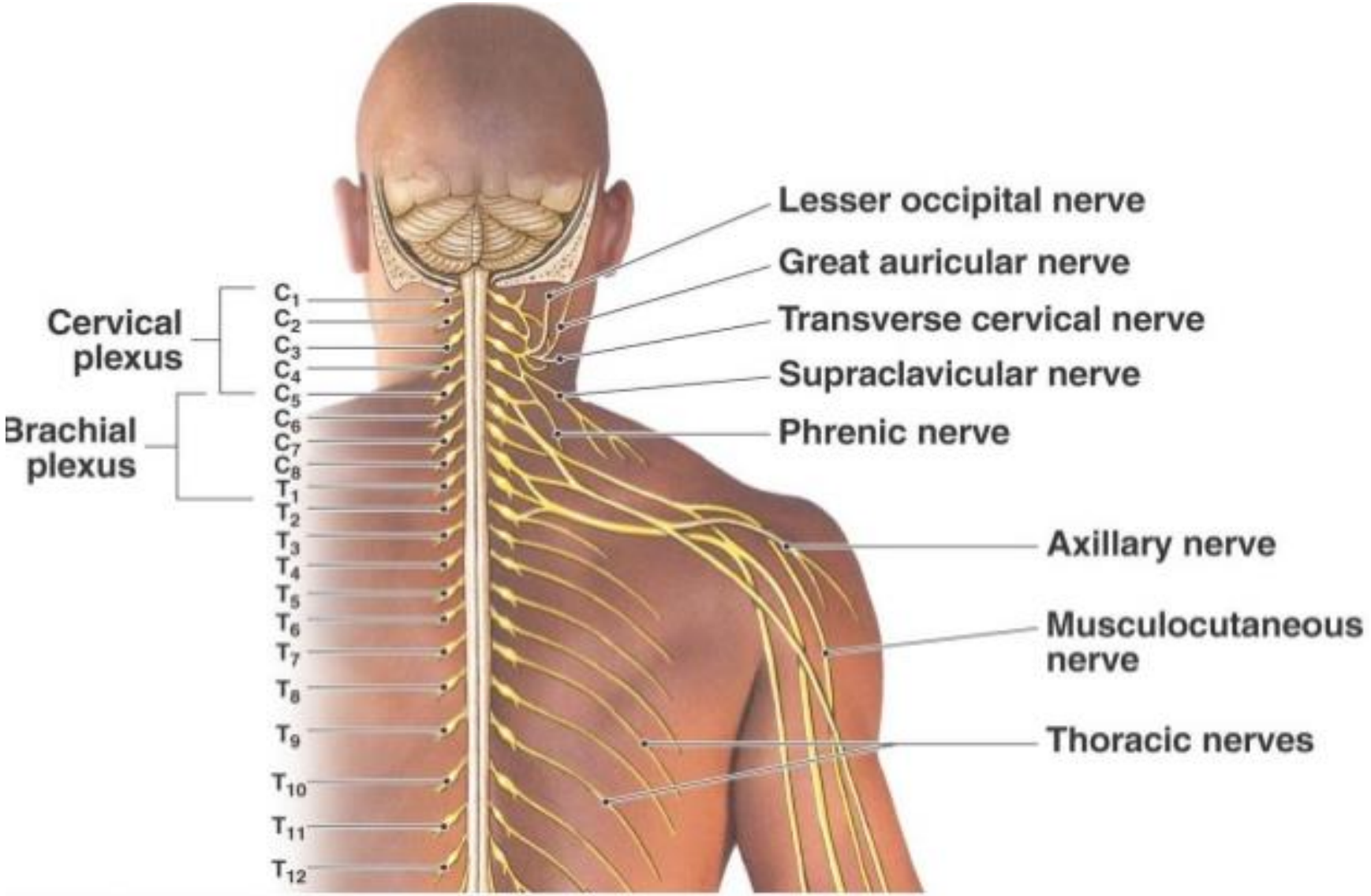
Injection site[1]

- Split the difference between injection 1 and the acromioclavicular joint

G3

Injection site[1]

- Split the difference between injection 1 and the necklace line


Cervical plexus
Brachial plexus
C1
C2
C3
C4
C5
C6
C7
C8
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
Lesser occipital nerve
Great auricular nerve
Transverse cervical nerve
Supraclavicular nerve
Phrenic nerve
Axillary nerve
Musculocutaneous nerve
Thoracic nerves

Take home message

- Clinical evidence: PREEMPT 1 & 2, COMPEL REPOSE; 50% RR: 50%, 75% RR: 25%
- Guidelines: CM, 2-3 failures
- PREEMPT protocol: 155/12wks
- Common AEs: neck pain/weakness, lateral eyebrow elevation, ptosis