Current diagnosis and treatment of chronic migraine

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Outline

- Introduction
- The Evolution of Chronic Migraine: Classification and Nomenclature
- Risk factors of Chronification & pathophysiology of CM
- Evidence treatment of CM

Part I : Introduction

- Migraine is a common, disabling disorder.

- While in most migraine patients the headaches occur episodically, some patients experience increasing headache frequency with time, until the attacks occur daily or almost daily.

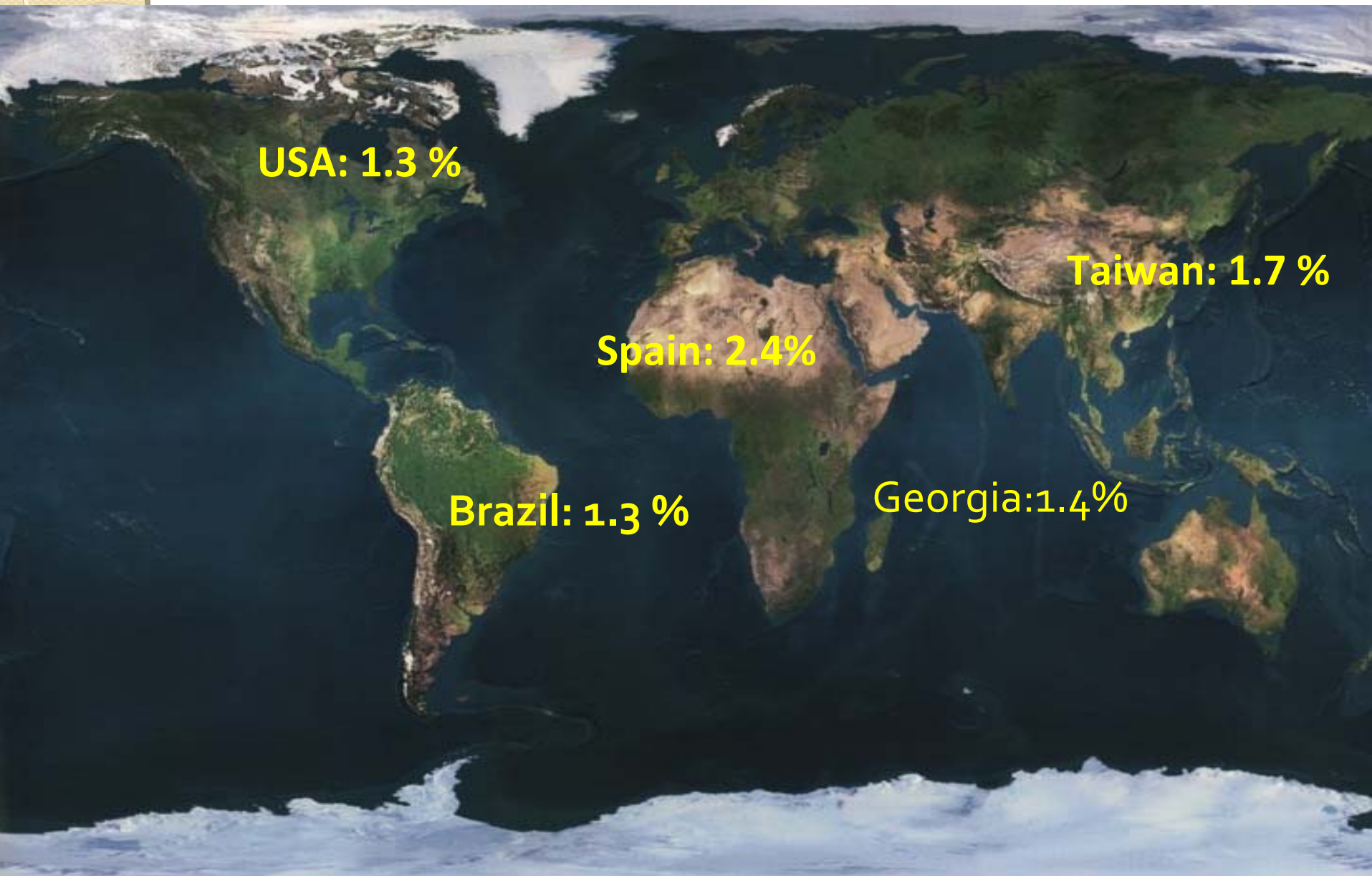
Main Menu

Prevalence of Migraine Globally

France	5-12%
Denmark	10%
Germany	11%
Italy	12%
Taiwan	9.1%
UK	7%
USA	9-12%

Adapted from Lipton RB, et al. *Headache*. 1994

Prevalence of Chronic Migraine Globally



"Chronic" ～ 頭痛小百科

In TACs (cluster, paroxysmal hemicrania, SUNCT)

Unremitting for ≥ **1** years or

remission period < 1 month

(時間很長)

In other headache disorders

On ≥ **15** days/month and for ≥ 3 months

(頻率很多)

Classification of primary "Chronic" headache

Duration ≥ 4 h/d

- Chronic migraine
- Chronic tension-type headache
- Hemicrania continua
- New daily persistent headache

Chronic daily headache

Duration <4h/d

Chronic cluster headache
Chronic paroxysmal hemicrania
SUNCT syndrome

Trigeminal autonomic Cephalalgia (TACs)

- Primary stabbing headache
- Hypnic headache

SUNCT = short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing

Chronic Daily Headache

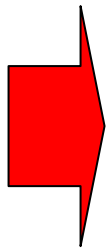
Four Major Forms

- Chronic (transformed) migraine (CM)
- Chronic tension-type headache (CTTH)
- Hemicrania continua (HC)
- New daily persistent headache (NDPH)

≥ 15 days/month

≥ 3 months

≥ 4 hours per day



Episodic: <15 days/month

CM an important issue..

- CM is the most common cause of CDH.
- This population are associated with significant disability, psychological distress, reduced health-related quality of life, and considerable healthcare cost .
- Acute medication overuse is reported in about 66% to 75% of adults with CM.

JNNP 2010,81;428-432

Part II

The Evolution of Chronic Migraine:

Classification and Nomenclature

必也正名乎…

- **After nearly 3 decades of debate, the headache community still lacks globally accepted criteria for *chronic migraine*.**

- **In order to be applicable to clinical practice and academic research, consensus on the optimal criteria for CM is needed.**

The Evolution of Chronic Migraine

- In 1987, the term transformed migraine was first used by Matthew.

- ICHD-1 (1988) was not comprehensive enough for patients with daily or near-daily migraine who were being seen in the clinic in large numbers.

*Cephalalgia 1985; 5(suppl 2): 191-3.

- Mathew's revision of his criteria for *transformed migraine* (1993)

- Silberstein and Lipton's * (1994,1996):
  - Chronic (transformed) migraine (CM)
  - Chronic tension-type headache (CTTH)
  - New daily persistent headache (NDPH)
  - Hemicrania continua (HC)

  ± **medication overuse**

- ICHD-II (2004): defined CM, CTTH, NDPH, HC, and medication-overuse headache (MOH)

- ICHD-II revised criteria for CM & MOH (ICHD-II$_R$, 2006)

*Headache 1994; 34: 1-7.

Classification and source	Description and/or diagnostic criteria	Limitations of proposed criteria
Transformed migraine Mathew, 1993	Patients who have clear-cut episodic migraine headaches that progress in severity and frequency. Clinically relevant subtypes include: (1) *transformed migraine* related to excessive drug use; and (2) *transformed migraine* unrelated to excessive drug use	Easily applied in general practice but lacked the reliability to support academic and epidemiological studies of disease state and progression

Classification and source	Description and/or diagnostic criteria	Limitations of proposed criteria
Transformed migraine Silberstein and Lipton Criteria, 1994	Daily or near-daily headache with migraine that begins with episodic migraines and as the headaches grow more frequent over months to years the associated symptoms become less severe and less frequent A. History of episodic migraine meeting any IHS criteria 1.1 to 1.6 B. Daily of almost daily (≥15 days/month) head pain for >1 month C. Average headache duration of >4 hours day (if untreated) D. History of headache frequency with decreasing severity of migrainous features over at least 3 months E. At least 1 of the following: 1. There is no suggestion of one of the disorders listed in groups 5-11 2. Such a disorder is suggested, but it is ruled out by appropriate investigations 3. Such a disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder	Limited in general practice by a dependence on a patient's recall of their headache transformation

Classification and source	Description and/or diagnostic criteria	Limitations of proposed criteria
Transformed migraine Silberstein and Lipton Criteria, 1996	Daily or near-daily headache with migraine that begins with episodic migraines and as the headaches grow more frequent over months to years the associated symptoms become less severe and less frequent A. Daily of almost daily (>15 days/month) head pain for >1 month B. Average headache duration of >4 hours day (if untreated) C. At least 1 of the following: 1. History of episodic migraine meeting any IHS criteria 1.1 to 1.6 2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months 3. Headache at some time meets IHS criteria for migraine 1.1 to 1.6 other than duration D. Does not meet criteria for new daily persistent headache or hemicrania continua E. At least 1 of the following: 1. There is no suggestion of one of the disorders listed in groups 5-11 2. Such a disorder is suggested, but it is ruled out by appropriate investigations	Requiring 1 criterion from category C was problematic because if C.2 applies to a patient but not C.1 or C.3 then a patient could be diagnosed with transformed migraine, but not have a history of episodic migraine or currently experiencing migraine headache

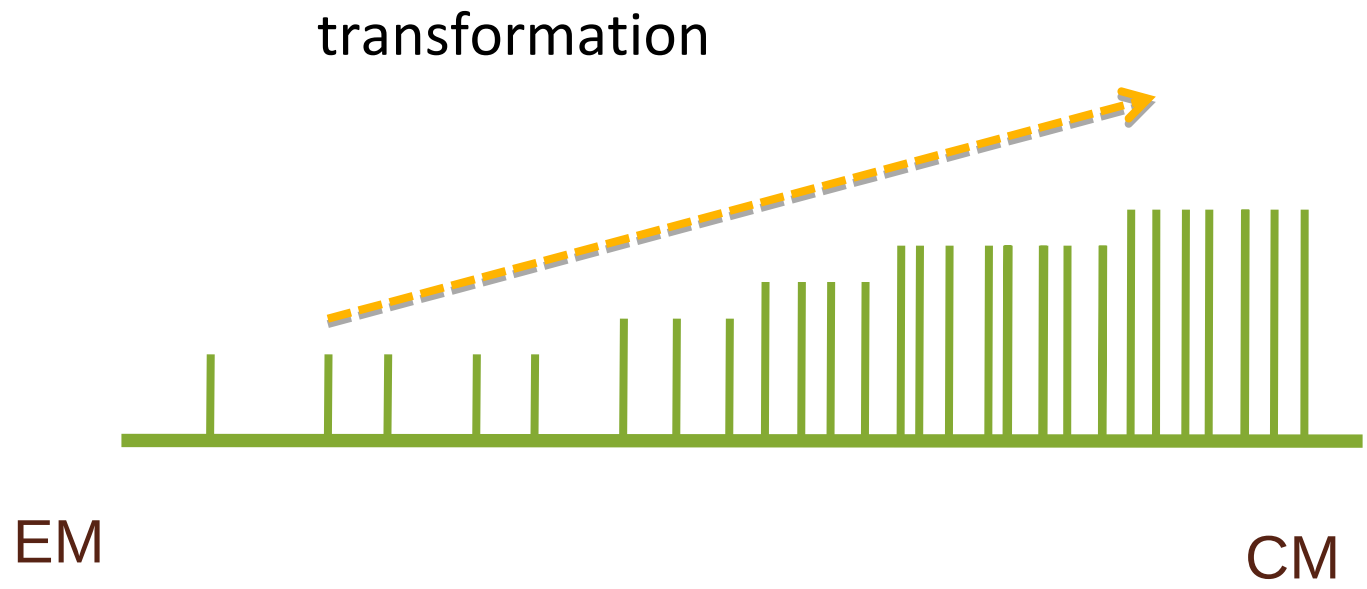
Classification and source	Description and/or diagnostic criteria	Limitations of proposed criteria
Chronic migraine Manzoni et al, 1995	Migraine with an unfavorable evolution without typical symptom-free intervals between attacks A. Fulfills criteria for migraine (IHS criterion 1.1) B. Headache for at least 6 days a week for at least 1 year	Lacks criteria or Stratification for medication overuse

Classification and source	Description and/or diagnostic criteria	Limitations of proposed criteria
Chronic migraine (original) ICHD-2, 2004	Migraine headache occurring on 15 or more days/month in the absence of medication overuse A. Headache fulfilling criteria C and D for migraine without aura on 15 days/month for >3 months B. Not attributed to another disorder†	Migraine on 15 days/month was too restrictive thus did adequately describe the majority of CM patients seen in Headache clinics and CM diagnosis was dependent on the absence of MOH which could only be diagnosed when a patient no longer had MOH

Classification and source	Description and/or diagnostic criteria	Limitations of proposed criteria
Chronic migraine (revised) ICHD-2 (revised), 2006	Frequently occurring headache (>15 days per month) with at least 8 days of migraine or probable migraine per month in the absence of medication overuse A. Headache (tension-type and/or migraine) on >15 days per month for >3 months B. Occurring in a patient who has had >5 attacks fulfilling criterion 1.1 migraine without aura C. On >8 days per month for >3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura 1. Has at least 2 of a-d: (a) unilateral location; (b) pulsating quality; (c) moderate or severe pain intensity; (d) aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs); and at least 1 of a or b: (a) nausea and/or vomiting; (b) photophobia and phonophobia 2. Treated and relieved by triptan(s) or ergot before expecting development of C1 above D. No medication overuse‡ and not attributed to another causative disorder†	Lacks universal acceptance because category D requirement is subject to the ongoing debate on whether chronic headache is a cause or consequence of medication overuse and category D is nearly impossible to assess in large scale epidemiological studies Category C2 is subject to patient's ability to recall relieve by triptan(s) or ergot before expecting development a migraine headache

≥75% CM experienced EM

Less nausea/vomiting
Less throbbing …



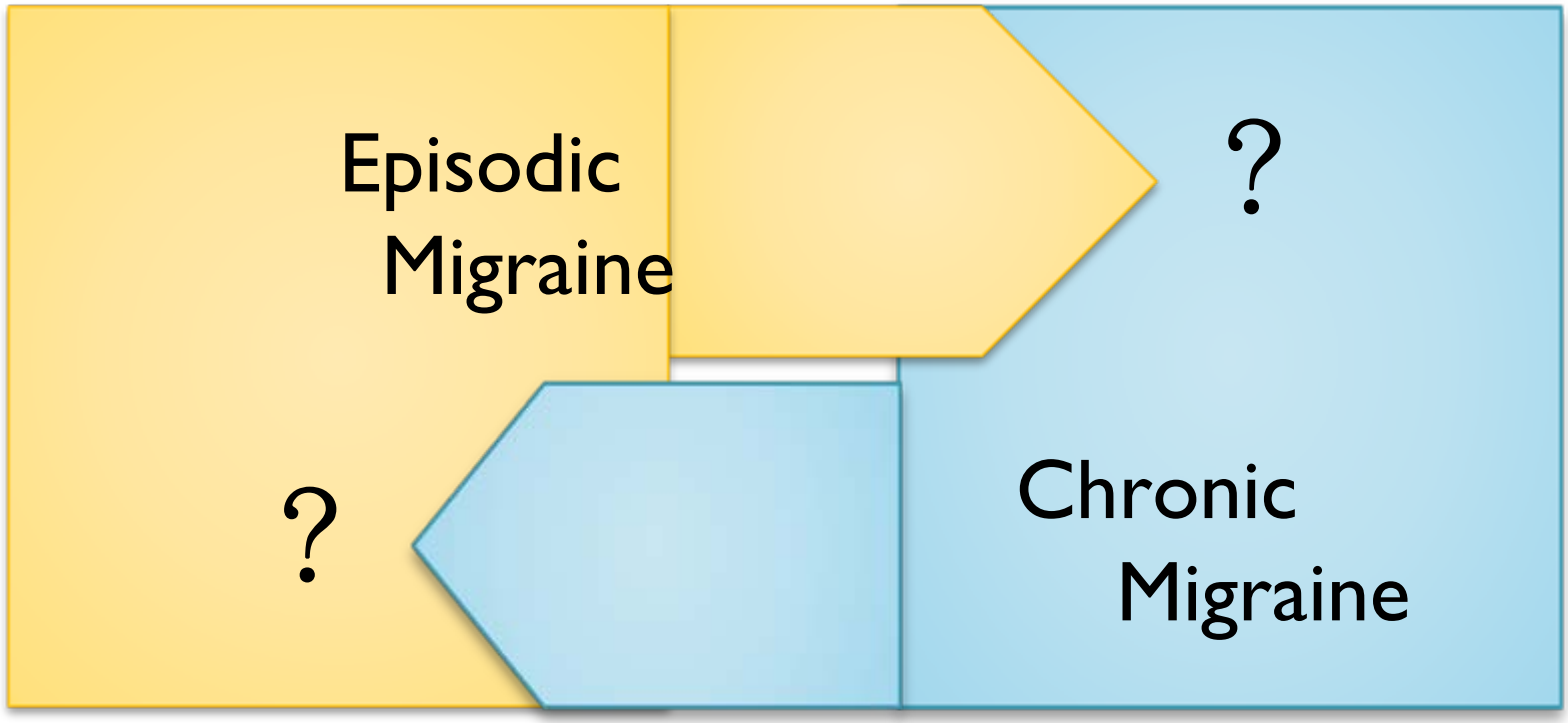
Headache. 2000;40:306-310.

Part III

Risk factors of chronification and

pathophysiology of CM

“Transform”



AMPP study

Table 2 Summary of sociodemographic and comorbidity differences between chronic and episodic migraine

Variable	Chronic migraine	Episodic migraine
Mean age, *y (SD)*	47.7 (14.0)	46.0 (13.8)
Race[a], %	78.6	80.0
Employment	1 in 5 reported being "occupationally disabled"	1 in 10 reported being "occupationally disabled"
Household income[b], %	29.9%	24.9%
Mean BMI, *n (SD)*	29.8 (8.3)	29.2 (7.9)
Cutaneous allodynia, %	68.2	63.2
Comorbid conditions	More likely to report or meet criteria for psychiatric, pain, respiratory, and cardiovascular comorbid conditions	Less likely to report or meet criteria for psychiatric, pain, respiratory, and cardiovascular comorbid conditions

American Migraine Prevalence and Prevention= AMPP

EM transform

- Based on AMPP study, among persons with episodic migraine in the US population, the incidence of CM in a subsequent year was 2.5%.
- In a prospective study from Germany, patients with EM in tertiary clinic populations are at risk of developing CDH, especially CM, over 1 year was 14%.
- In a long-term, retrospective, clinic-based study of persons with one to six attacks per month of episodic migraine, 1.6% had developed CM at 10 years post assessment.

Neurology 2004, 62:788–790.

Headache 2008, 48:1157–1168. Headache 2009, 49:1144–1152.

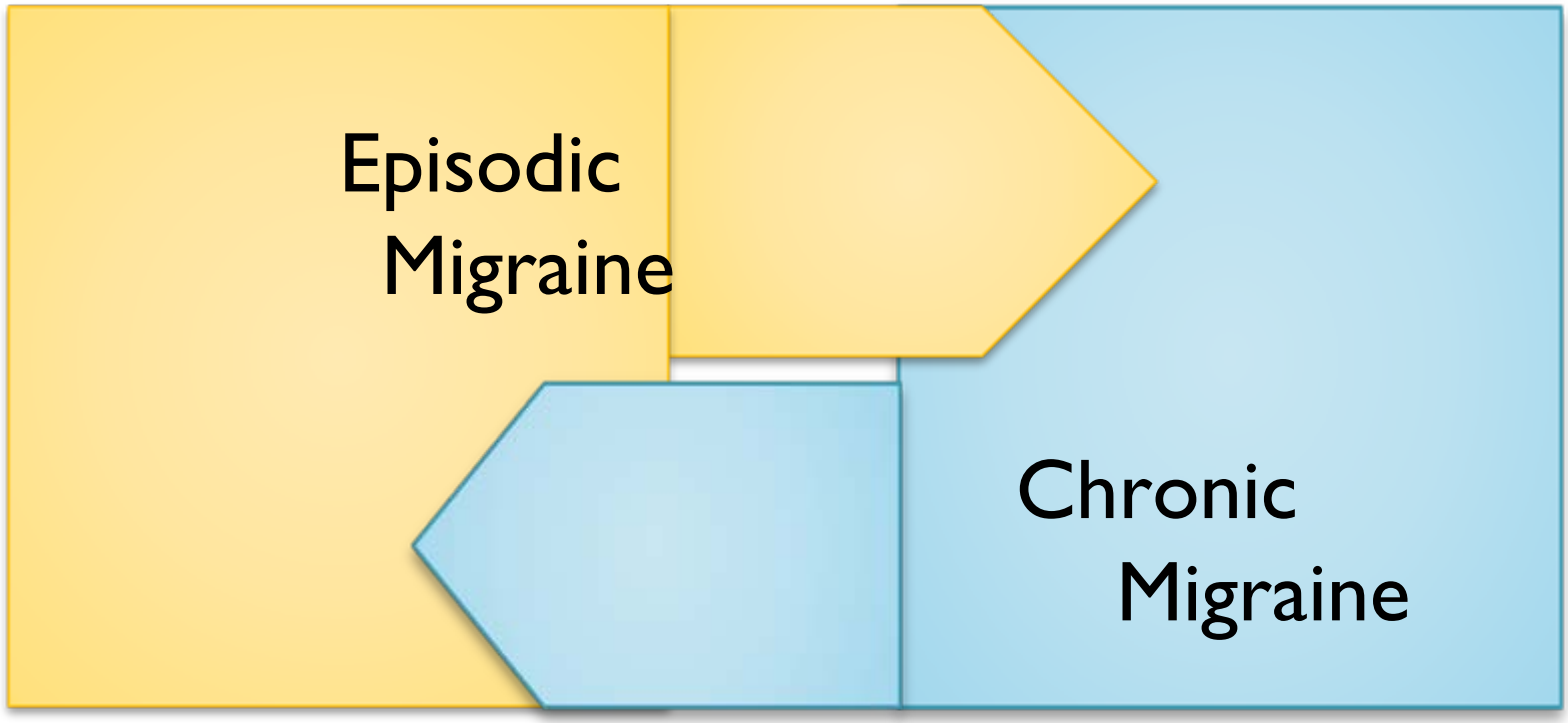
CM Remission

- Data are limited on the remission of chronic migraine.
- AMPP study concluded that approximately 25%. of those with CM remitted to EM or other headache types over the course of 2 years.

- Predictors of remission included headache frequency (average days/mo) and the absence of allodynia.

Neurology 74 (Suppl 2):A113, 2010.

“Dynamic”



Fluctuate between chronic and episodic headache patterns

Risk factors for CM "Chronification"

Non modifiable

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

Modifiable

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

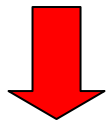
Putative factors

- Proinflammatory or prothrombotic states

Current Pain Headache Report 2009; 13: 59-63

Baseline attack frequency

- Patients with a high baseline headache frequency of 5 to 9 days per month have a substantially increased risk for progression to a chronic headache condition.
- This risk is further increased in patients with a "critical" headache frequency, defined as more than 10 -14 days per month.

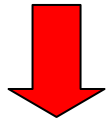


- This implies that reductions in migraine attack frequency may reduce the risk of developing CM.

Intern Emerg Med (2010) 5 (Suppl 1):S13–S19

Obesity

- Overweight individuals (BMI:25–29) have a threefold higher risk of developing CM.
- Obesity (BMI> 30),have a five times greater chance of developing CDH as compared to individuals with a normal weight.



- In obese patients with EM, weight reduction might prevent the progression to chronic migraine; however, no studies have specifically investigated weight reduction as a therapeutic intervention in CM.

Neurology 2006; 67:252–257.

Pathogenesis of CM

- The pathophysiology of CM is not clear.
- Recurrent migraine attacks as a cause for structural and functional changes in CNS (iron deposition in PAG; white-matter lesions in the posterior circulation infarcts)
- Sensitization of central trigeminothalamic pathways is considered one possibility.
- Dysmodulation from impaired descending inhibition or enhanced descending facilitation of nociception are possibilities.
- The frequent overuse of acute pain medications also may play a major role in the development of CM.

Curr Opin Neurol. 2002;15:287-295. *JAMA.* 2004;291:427-434.

Part IV

Evidence treatment of CM

Goals of preventive therapy for CM

- The ultimate goal should be allowing CM to revert back to EM, or preventing the development of CM in the first place.

Management of CM

- Identifying and managing risk factors (eg, sleep apnea, caffeine consumption)
- Assessing and treating neuropsychiatric disorders and other comorbid conditions that could contribute to increased attack frequency.
- limits on acute pain medications to less than 10 days per month
- Preventive treatment should be individualized based on comorbid or coexistent illness/disorders, specifically avoiding drugs that may exacerbate another underlying condition.

Current evidence of treatment for CM

- Migraine research has traditionally focused on EM, but recent clinical trials have started to focus on CM or CDH.
- Up to now, only topiramat and local injection of botulism toxin have been shown to be effective in placebo-controlled randomized trials for prophylaxis.
- Both therapies are effective in patients with CM with and without medication overuse.

Clinical trials summary: Double-Blind Placebo Controlled Trials in CM/CDH

- Gabapentin (2,400mg) Spira 2001 (133CDH)
- Tizanidine (median 20mg) Saper 2002(134 CDH)
- Sodium valproate (1,000mg)Yurekli 2008 (70 CDH, 29 CM)
- Topiramate (50 mg) Silvestrini 2003 (28 CM)
- Topiramate (50-100mg) Mei 2006 (50 CM)
- Topiramate (100 mg) Diener 2007 (59 CM)
- Topiramate (86.0 mg) Silberstein 2007 (328 CM)

- All trials were positive

Neurol Sci (2010) 31 (Suppl 1): S23-S28

Topiramate in the treatment of chronic migraine

M Silvestrini[1,2], M Bartolini[1], M Coccia[1], R Baruffaldi[1], R Taffi[1] & L Provinciali[1]
[1]*Department of Neurological Sciences, University of Ancona, Ancona, Italy,* [2]*IRCCS, S. Lucia, Rome, Italy*

- double-blind, placebo-controlled.
- 28 CM with acute medication overuse.
- 50 mg/d.
- 8 weeks.
- Baseline headache days TPM(20.9±3.2);Placebo (20.9±3.2).
- lower headache frequencies compared to those treated with placebo (mean 8.1±8.1 headache days, vs 20.6±3.4 headache days).
- 71% responder rate (≥ 50% improvement in monthly headache frequency) for TPM versus a 7% placebo response rate.

Cephalalgia. 2003, 23:820–824.

Topiramate and Triptans Revert Chronic Migraine With Medication Overuse to Episodic Migraine

Daniele Mei, MD, PhD,† Diana Ferraro, MD,* Giovanni Zelano, MD,†‡*
Alessandro Capuano, MD, Catello Vollono, MD,**
*Carbone Gabriele, MD,† and Girolamo Di Trapani, MD**

Randomized, double-blind. Placebo controlled
35 CM with MO according to ICHDII
100 mg/d
12 weeks
TPM had a significant reduction in the number of days with headache and in the mean amount of acute medication taken (all P<0.05 vs placebo)

Clin Neuropharmacol 2006;29:269-275

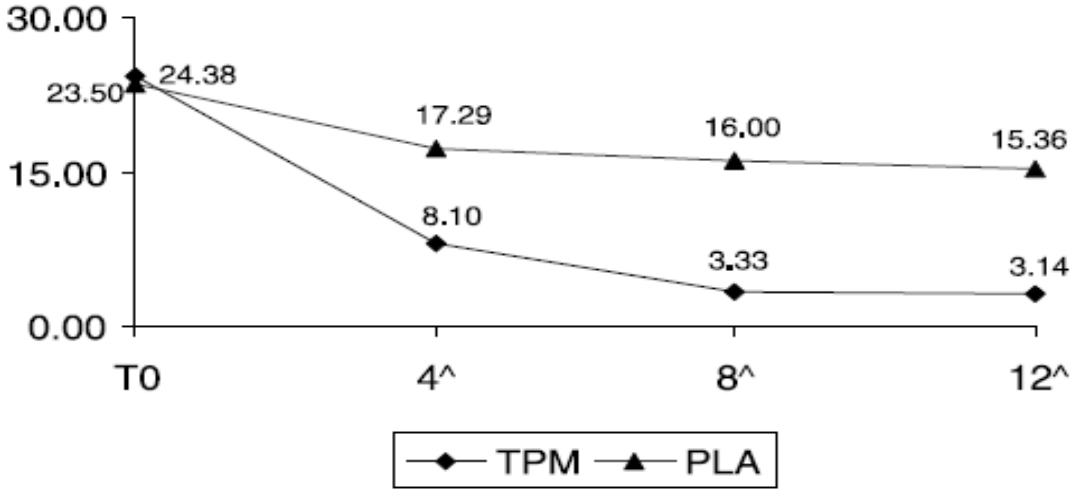


FIGURE 1. Effects on the number of monthly days with headache.

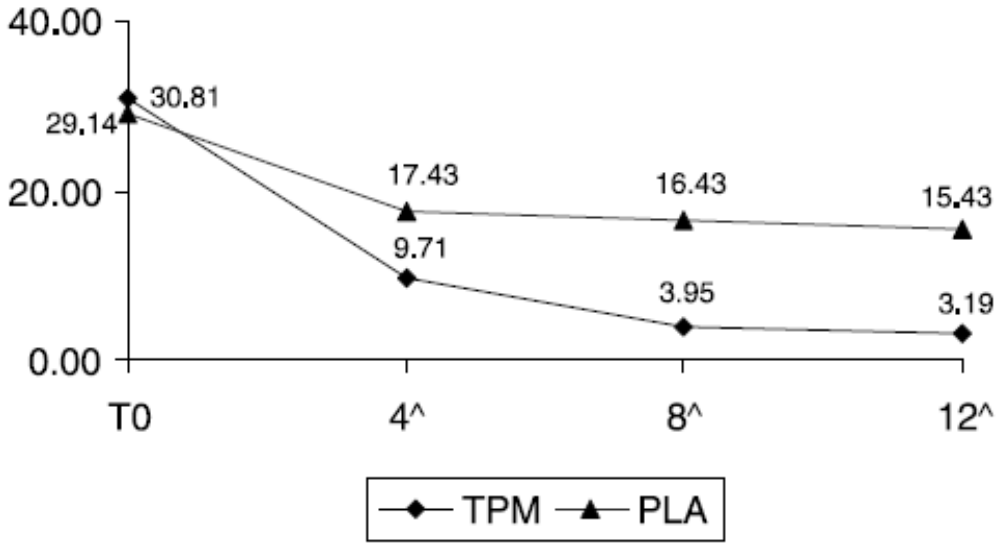


FIGURE 2. Effects on the amount of acute medication taken monthly.

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

- 59 CM
- Most patients (78%) met the definition of MOH
- flexibility from 50 to 200 mg/day (average:100 mg/d)
- 16 weeks
- Baseline migraine days TPM (15.5±4.6); Placebo (16.4±4.4).
- TPM significantly reduced the mean number of monthly migraine days by -3.5±6.3, compared with placebo (-0.2±4.7, $P < 0.05$).
- 22% responder rate in TPM; 0% responder rate in placebo.
- No significant intergroup differences were found for MSQ and HIT-6.
- MIDAS showed improvement with the TPM group ($P = 0.042$ vs. placebo).

Cephalalgia, 2007, **27**, 814–823

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

- 306 CM
- maximum of 100 mg/day (mean final:86mg)
- **mean duration of therapy:TPM(91.7 day); placebo(90.6 day)**
- Baseline migraine/migrainous headache days TPM (17.1 ± 5.4); Placebo (17.0 ± 5.0).
- TPM resulted in a statistically significant mean reduction of migraine/migrainous headache days (TPM -6.4 vs placebo -4.7 , $P = .010$).

Headache 2007;47:170-180

AEs

- In these TPM studies, adverse events in CM patients were similar to those reported in previous trials on EM patients, and included paresthesia, fatigue, anorexia, nausea, diarrhoea, weight loss, dizziness, taste perversion, and difficulties with memory and concentration.
- The most common adverse events were paresthesia (30–50% patients), and fatigue (6–11%).

REVIEW

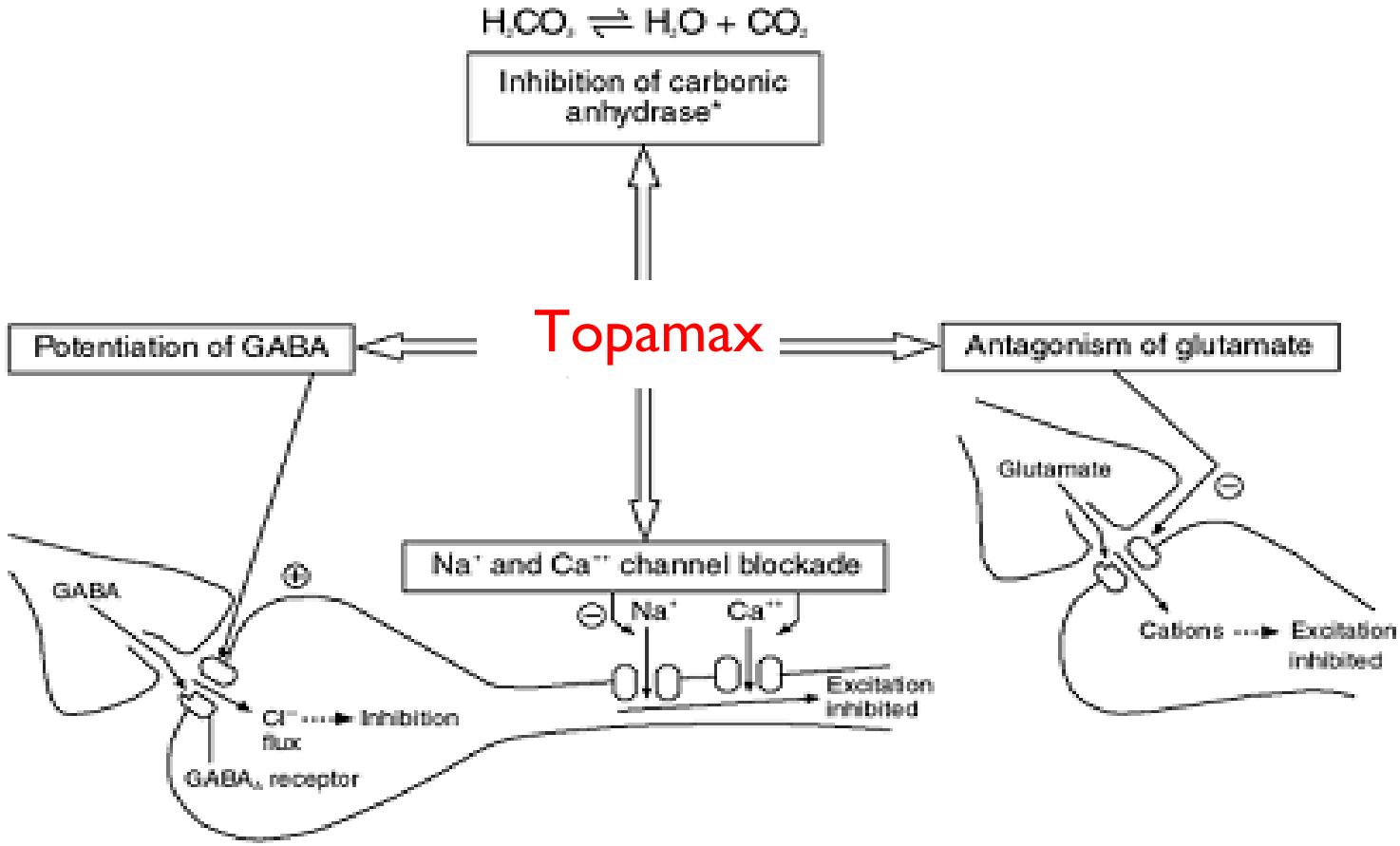
Utility of topiramate for the treatment of patients with chronic migraine in the presence or absence of acute medication overuse

H-C Diener[1], DW Dodick[2], PJ Goadsby[3], ME Bigal[4]*, G Bussone[5], SD Silberstein[6], N Mathew[7], S Ascher[8], J Morein[8], JF Hulihan[8], DM Biondi[8] & SJ Greenberg[9]†

- Both studies demonstrate the efficacy and safety of TPM for the treatment of CM in patient populations both with and without MO.
-
- These studies may have important implications for the future of CM management, suggesting that detoxification prior to initiating prophylactic therapy may not be required in all patients if MO is present.

Cephalalgia, 2009, **29**, 1021–1027

Comprehensive Mechanisms



* Inhibition of carbonic anhydrase has not been experimentally established as an anticonvulsant mechanism

Shank R P et al. Epilepsia. 2000;41(suppl 1):S3.

Epilepsia. 2000;41(suppl 1):S3.

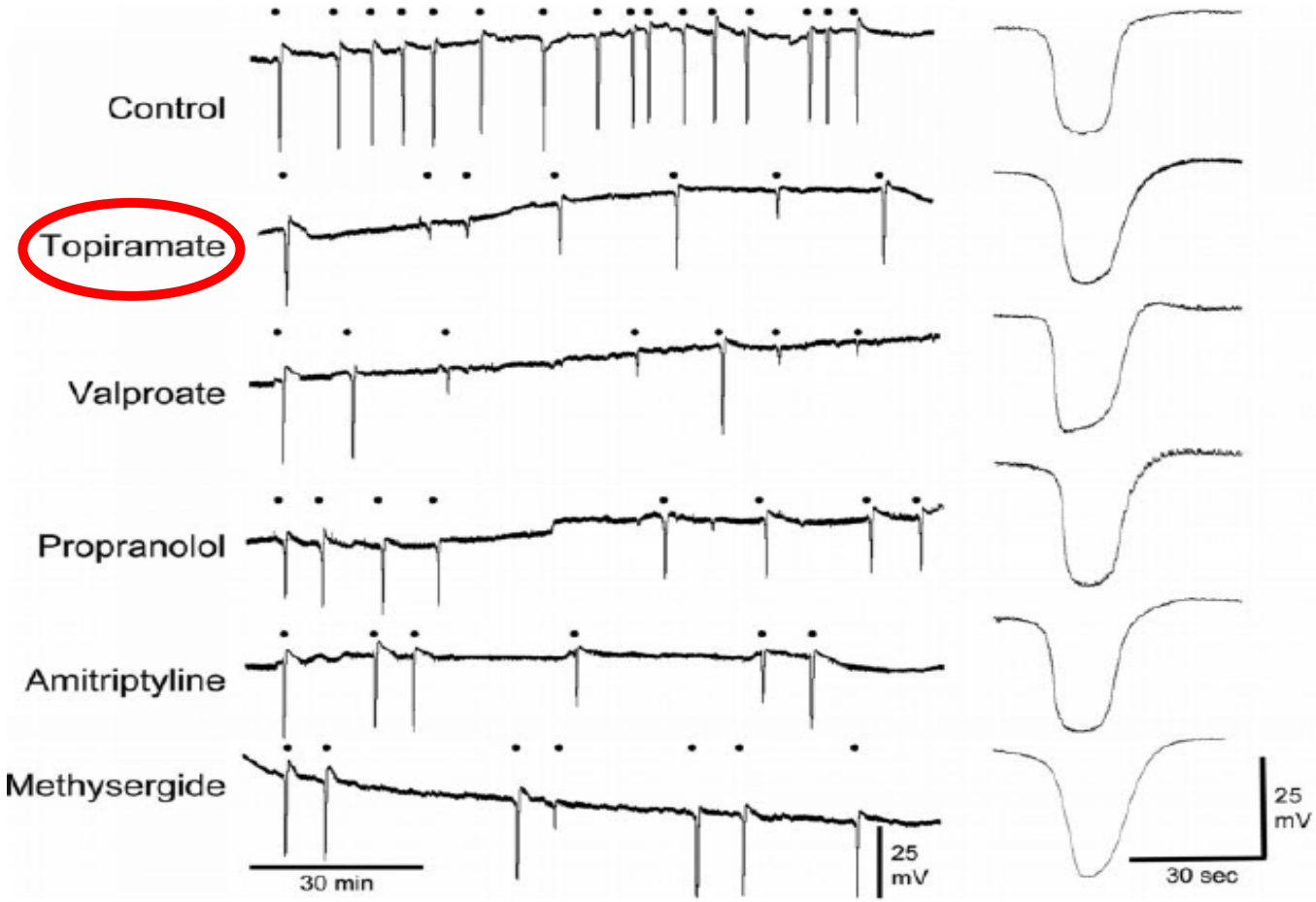
Possible mechanisms of TPM

- It is through these mechanisms to reduce cortical neuronal hyperexcitability, which is believed to be an important electrophysiological feature underlying the pathogenesis of epilepsy and migraine.

- TPM acts by reducing nociceptive transmission at the central system level through inhibition of the cortical spreading depression (CSD).

Cephalalgia 24:735–739 Int Emerg Med 2009;4:367–373

Inhibition of CSD after chronic treatment with migraine prophylactic drugs



Ann Neurol 2006;59:652–661

Topiramate in Patients With Episodic Migraine: Reducing the Risk for Chronic Forms of Headache

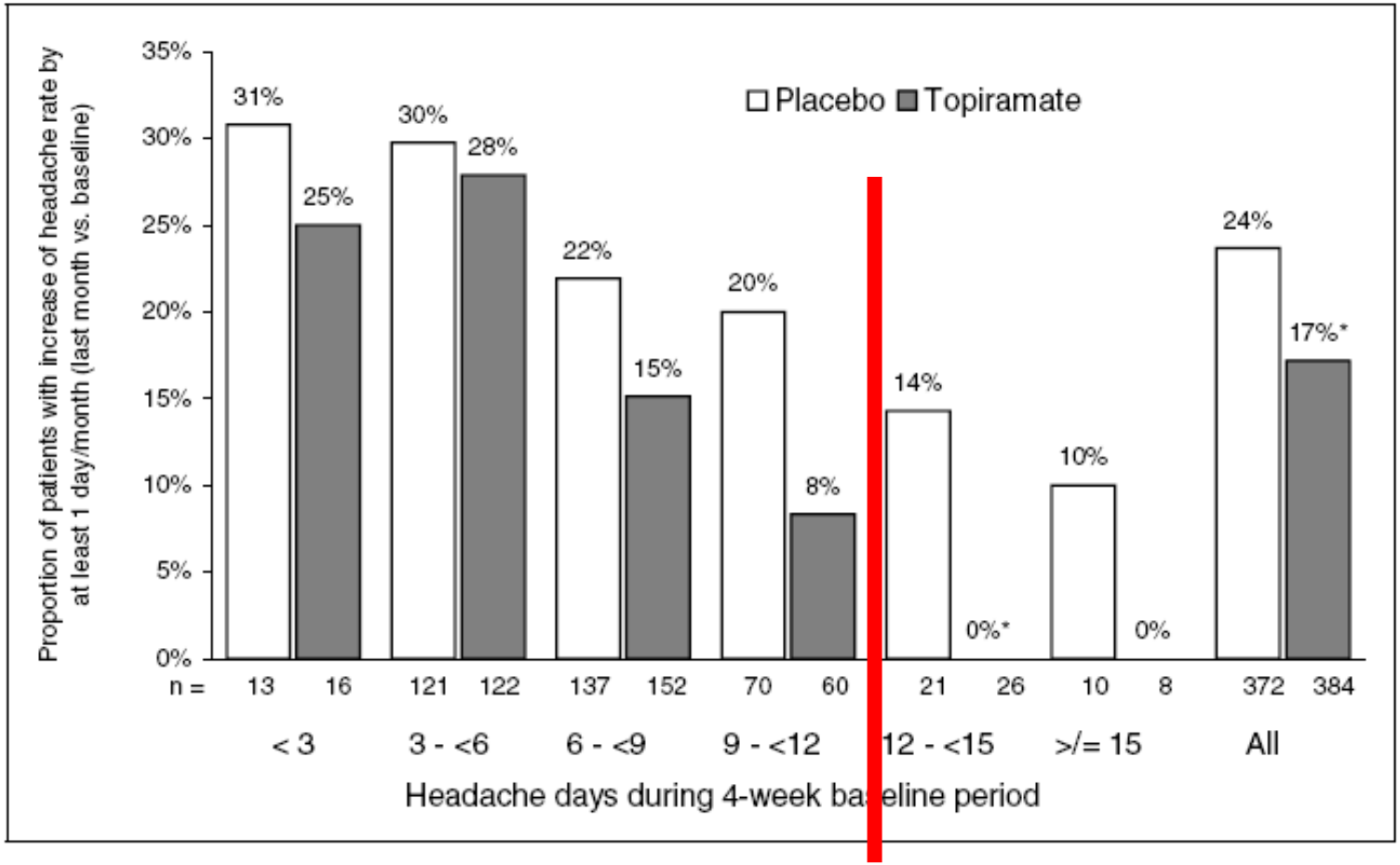
Volker Limmroth, MD; David Biondi, DO; Joop Pfeil, MSc; Susanne Schwalen, MD

- Pooled data from 3 trials in patients with EM.
- 100mg TPM per day (n=384) or with placebo (n=372)
- 26 weeks
- fewer patients in TPM group experienced an increase in the number of headache days 66 vs 88 (OR = 1.45, p=0.05)
- Preventive treatment with TPM resulted in a significant reduction in the use of acute medication compared with placebo.
- high-risk patients (≥12 days) appear to benefit most from preventive treatment with TPM.
- Conclusion:

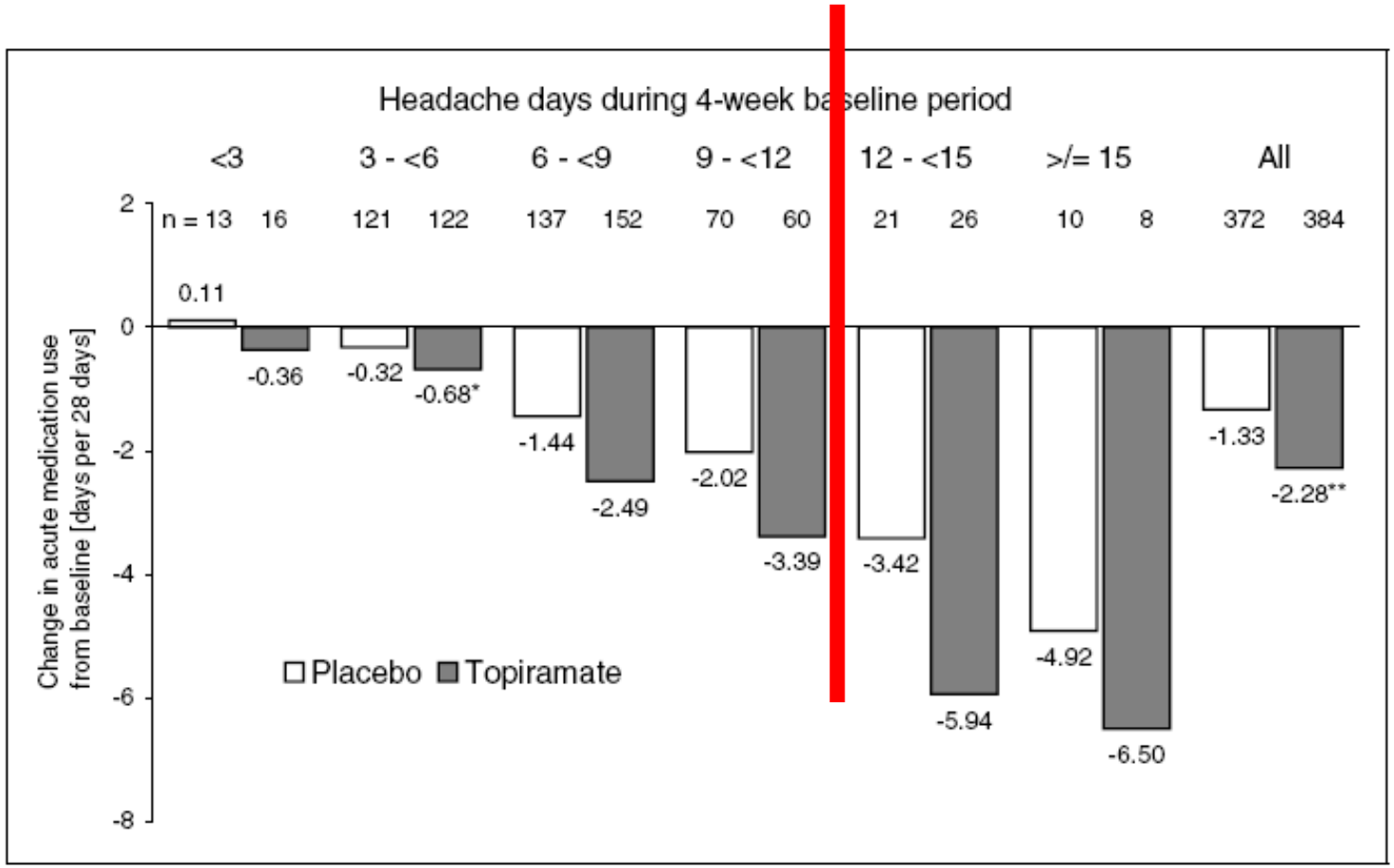
  Preventive treatment with TPM in patients with EM may reduce the risk of developing CM.

Headache 2007;47:13-21

headache days per month increased by at least 1 day in comparison with baseline



mean change in the number of days with acute medication use per month



The evidence of BTX for CM

- Despite positive open-label studies and case reports, BTX has not proven to be effective for many patients with ETTH,CTTH or EM based on double-blind placebo-controlled trials.
-
- These results could have been confounded by a high placebo response rate.
- There is increasing evidence, however, that BTX is effective in the treatment of CDH especially subtype of CM.

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY 60th ANNIVERSARY

Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review)

Neurology 2008;70:1707-1714

Table Botulinum neurotoxin (BoNT) for autonomic disorders and pain

Disorder	Class	Outcome measures	Adverse events	Conclusions	Recommendations*	Limitations
Axillary hyperhidrosis	2 Class I	Gravimetry; responder rate; patient satisfaction	No difference between BoNT and placebo	Safe and effective	A	No head-to-head comparisons with other treatment options
Palmar hyperhidrosis	2 Class II	Gravimetry; ninhydrin test; VAS	Injection pain; mild hand muscle weakness	Probably effective	B	No head-to-head comparisons with other treatment options
Gustatory sweating	5 Class III	Area of sweating; ninhydrin test; self assessment	Injection pain	Possibly effective	C	No head-to-head comparisons with other treatment options
Drooling	4 Class II	Drooling scores; weight of dental roles; VAS	Dry mouth	Probably effective	B	No head-to-head comparisons with other treatment options
Detrusor overactivity	2 Class I and 1 Class II	Urodynamic measures; QOL; frequency of incontinence	Urinary retention	Safe and effective	A	No head-to-head comparisons with other treatment options
DSD in spinal cord injury	2 Class II	PRUV	None known	Probably effective	B	No head-to-head comparisons with other treatment options
Low back pain	1 Class II	VAS; Owestry low back pain questionnaire	None known	Possibly effective	C	Diverse etiologies for low back pain
Episodic migraine	2 Class I and 2 Class II	Change in frequency per month; proportion with 50% decease in frequency compared with baseline	Ptosis, local transient pain at the site of injection, bruising, diplopia	Probably ineffective	B	Suboptimal dose and muscle selection may account for treatment failures
Tension-type headache	2 Class I	VAS; area under the curve; proportion of severe headaches post treatment	Transient weakness of neck muscles, local skin tension, ptosis , flulike reaction	Probably ineffective	B	Suboptimal dose and muscle selection may account for treatment failures
Chronic daily headache	4 Class II	Change in headache-free days	Ptosis, transient weakness of neck, flulike reaction	Insufficient evidence	U	Suboptimal dose and muscle selection may account for treatment failures

Clinical Trial Summary: Onabotulinumtoxin A

- 2 open-label studies
  -Botox therapy for refractory chronic migraine. (Headache 2005;45:355-357)
  -Botulinum toxin type A in refractory chronic migraine: an open- label trial. (Arq Neuropsiquiatr 2007;65:596- 598)

- 1 small placebo-controlled study
  - Botulinum toxin type A in the treatment of CM without medication overuse. (Headache 2008;48:201-209)

- 2 large placebo-controlled studies:
  - Cephalalgia. 2010 ;30:793-803. **PREEMPT 1**
  - Cephalalgia. 2010;30:804-14. **PREEMPT 2**
  - Headache. 2010;50:921-36. **Pooled results**

PREEMPT Study: Phase III REsearch Evaluating Migraine Prophylaxis Therapy with Botulinum Toxin Type A

PREEMPT-1:

- January 23, 2006 to July 16, 2008
- 56 North American sites
- 619 CM±MOH

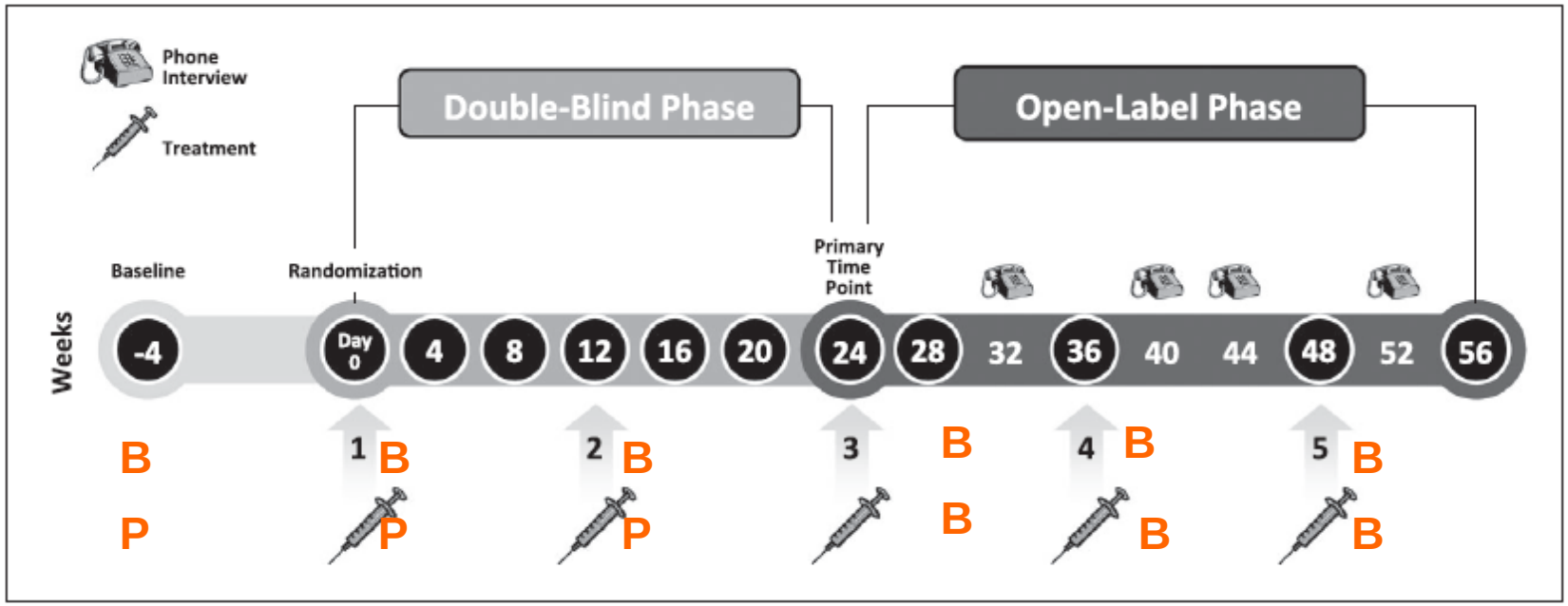
PREEMPT-2:

- February 7, 2006 to August 11, 2008,
- 66 global sites (50 North American and 16 European)
- 705 CM±MOH

Pooled Data:

- 1384 CM±MOH

PREEMPT Study Design



B: BoNT A

P: Placebo

Criteria & Endpoint

PREEMPT 1:

- Primary endpoint: frequency of headache episodes per month (28 days) at week 24

PREEMPT 2:

- Primary endpoint: frequency of headache days per month (28 days) at week 24

Inclusion criteria:

-ICH D2
-18-65 years

Exclusion criteria:

-Continuous headache
-No preventive medication for headache for 4 weeks
-BDI >24

Patients could continue their acute medication

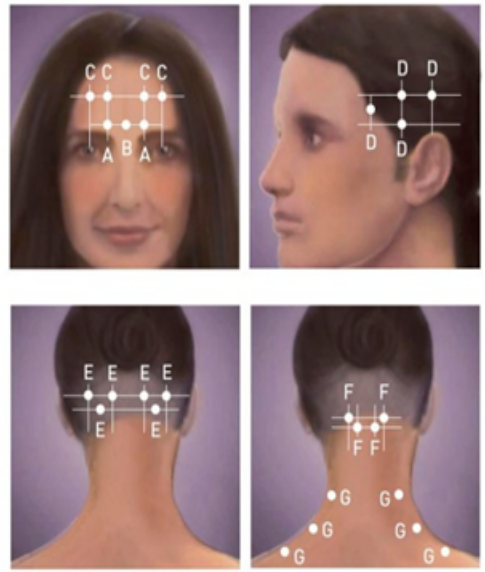
Pooled data (PREEMPT 1 and 2) 56-week study:

- Primary endpoint:
  - frequency of headache days per month (28 days) at week 24
- Secondary endpoints:
  - frequency of migraine days,
  - frequency of moderate/severe headache days,
  - total cumulative headache hours on headache days,
  - proportion of patients with severe (≥60) Headache Impact Test (HIT)-6 mean daily headache impact score,
  - frequency of headache episodes,
  - frequency of migraine episodes, and
  - frequency of acute headache medication use per month (28 days) at week 24

Injection Paradigm

PREEMPT: Fixed-site, fixed-dose and follow-the-pain protocol

- Fixed-site, fixed-dose are mandatory injections: 155 U (see table)
- Follow-the-pain refers to optional injections, depending on the severity and location of the pain: up to 40 U (see table)
- One dosing cycle represents 31 to 39 injections every 12 weeks
- Recommended reconstitution of BOTOX® (100 U):
  - 2 mL of preservative-free normal saline (0.9% sodium chloride, USP)
    - ✓ Final concentration: 5 U/0.1 mL
  - Inject immediately or store in refrigerator for up to 24 hours as per US label
- Injection protocol:
  - Injections performed with a 30-gauge, half-inch needle
  - Administer 0.1 mL (5 U) at each injection site
  - Total number of units administered: 155 U to 195 U
- The potency units of BOTOX® are not interchangeable with other preparations of botulinum toxin products



Order	Muscle	Fixed-Site, Fixed-Dose (U)	Follow-the-Pain (U)
A	Corrugator	10 (5 each side)	NA
B	Procerus	5	NA
C	Frontalis	20 (10 each side)	NA
D	Temporalis	40 (20 each side)	10 (up to 2 sites)
E	Occipitalis	30 (15 each side)	10 (up to 2 sites)
F	Cervical paraspinal	20 (10 each side)	NA
G	Trapezius	30 (15 each side)	20 (up to 4 sites)
Total number of units (U) =		155	195

NA = no additional

Pooled Data: Baseline Demographics

2/3 previous prophylaxis failure

2/3 with MOH

Baseline Patient Demographics and Characteristics

	BOTOX® (n=688)	Placebo (n=696)
Mean age, years	41.1	41.5
Mean years since onset of Chronic Migraine	19.4	19.0
Female, %	87.6	85.2
Caucasian, %	89.7	90.5
Mean HA days during baseline	19.9	19.8
Mean migraine days during baseline*	19.1	18.9
Mean moderate/severe HA days during baseline	18.1	18.0
Mean cumulative hours of HA occurring on HA days during baseline	295.93	281.22
% Patients with severe (≥60) HIT-6 score during baseline†	93.5	92.7
Mean HA episodes during baseline	12.2	13.0
Mean migraine episodes during baseline*	11.4	12.2
% Patients who had previously used 1 or more HA preventive medications	61.8	65.2
% Patients overusing acute medications during baseline‡	64.8	66.1
Mean HIT-6 score during baseline†	65.5	65.4

Pooled Data: Primary and Secondary Endpoints at Week 24

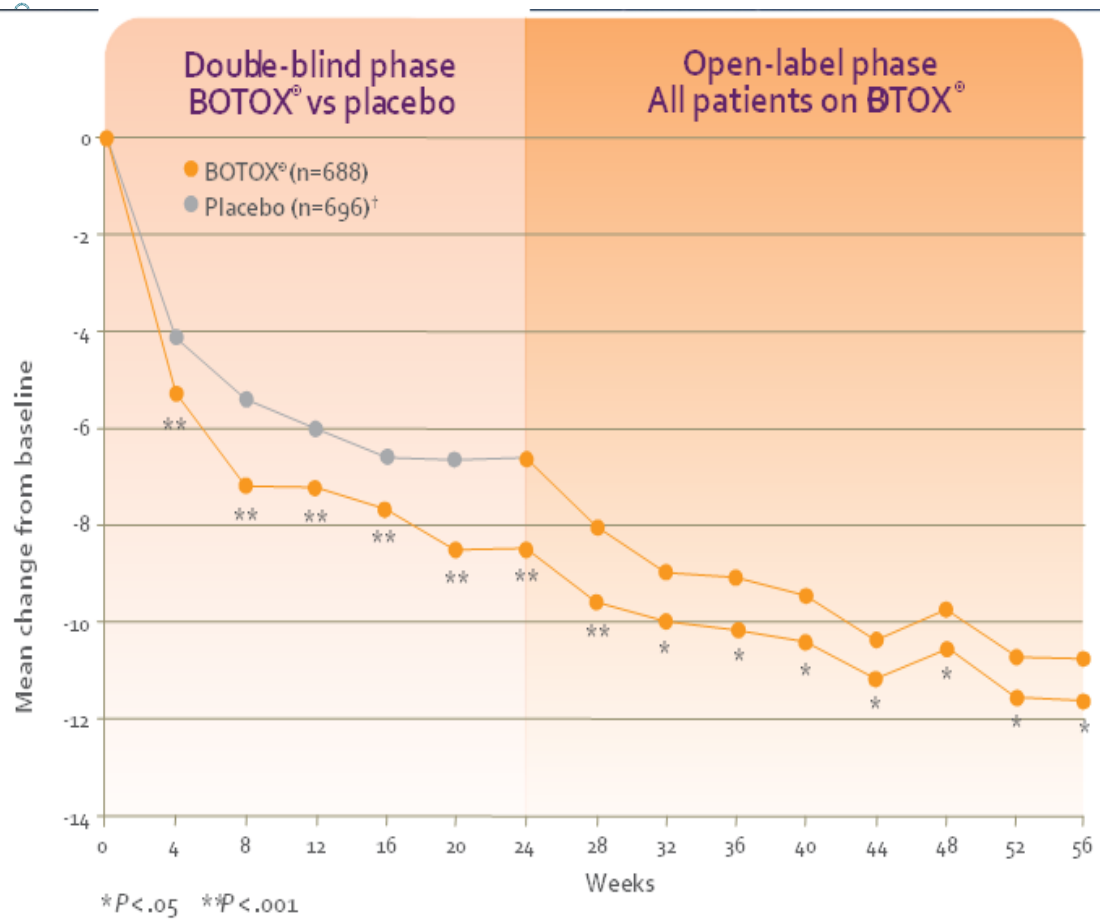
Pooled Efficacy of BOTOX® at Week 24 (Primary Time Point)

Endpoint, Mean Change From Baseline	BOTOX® (n = 688)	Placebo (n = 696)	*P* Value*
Frequency of HA days	-8.4	-6.6	<.001
Frequency of migraine days†	-8.2	-6.2	<.001
Frequency of moderate/severe HA days	-7.7	-5.8	<.001
Total cumulative HA hours on HA days	-119.7	-80.5	<.001
% Patients with severe (≥60) HIT-6 score‡	67.6	78.2	<.001
Total HIT-6 score‡	-4.8	-2.4	<.001
Frequency of HA episodes	-5.2	-4.9	.009
Frequency of migraine episodes	-4.9	-4.5	.004
Frequency of acute medication intake (all categories)	-10.1	-9.4	.247
Frequency of triptan use§	-3.2	-2.1	<.001

HA = headache; HIT = Headache Impact Test.
**P* values are from analyses of covariance (ANCOVA) with baseline as covariate. The main effects are treatment and medication overuse stratification.
†ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine).
‡Scores of 36–49 indicate little or no impact; 50–55, some impact; 56–59, substantial impact; ≥60, severe impact.
§Frequency of triptan use was not a secondary endpoint.

- 47% of patients on BOTOX® achieved ≥50% reduction in the number of headache days per month compared to baseline
- Patients treated with BOTOX® averaged 8 fewer migraine days per month compared to baseline
- BOTOX® significantly reduced headache-related disability and improved functioning and overall quality of life for patients suffering from Chronic Migraine

Pooled Data: Double-Blind and Open-Label Phases



†The n value shown for placebo represents the population treated with placebo during the double-blind phase, followed by BOTOX® in the open-label phase (placebo/BOTOX® population)

- BOTOX® provides sustained relief for Chronic Migraine sufferers
- During the double-blind phase, BOTOX® demonstrated significant improvement vs placebo
  - This improvement was sustained during the open-label phase
- Nearly 70% of patients treated with BOTOX® through the 56-week study period achieved ≥50% reduction in the number of migraine days from baseline

Discontinuation Rates and Treatment-Related Adverse Events

Discontinuation rates due to adverse events (AEs), pooled data, double-blind phase

BOTOX® (n=687)	Placebo (n=692)
3.8%	1.2%

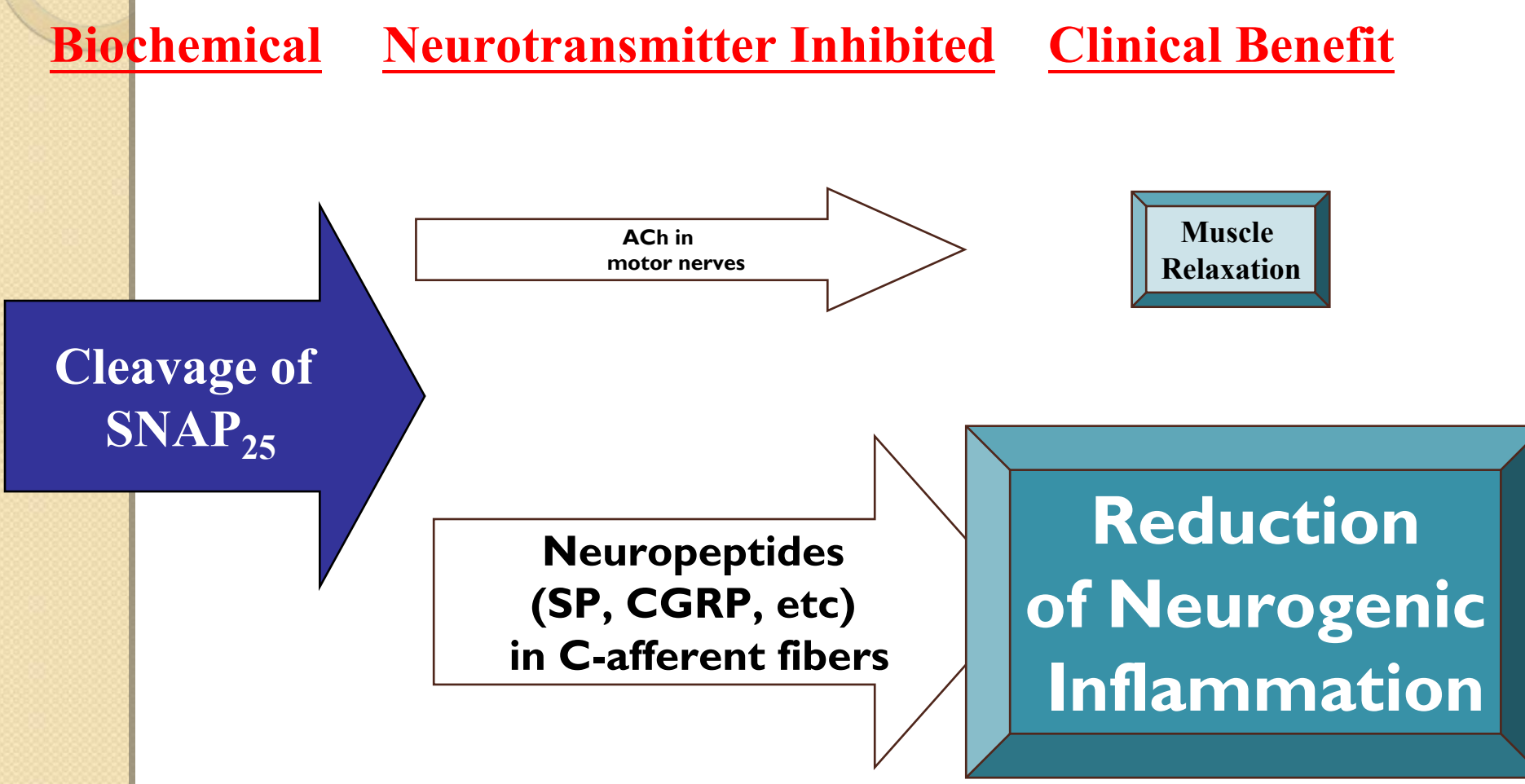
The results from PREEMPT demonstrate that treatment with 155 U to 195 U of BOTOX® every 12 weeks was well tolerated up to 5 cycles

Treatment-related AEs reported in ≥2% of patients pooled data, double-blind phase[1] (%)	(n=687)	Placebo (n=692)
Neck pain	6.7	2.2
Muscular weakness	3.5	0.3
Eyelid ptosis	3.2	0.3
Musculoskeletal pain	2.2	0.7
Injection-site pain	3.2	2.0
Headache	2.8	1.6
Myalgia	2.6	0.3
Musculoskeletal stiffness	1.9	0.7

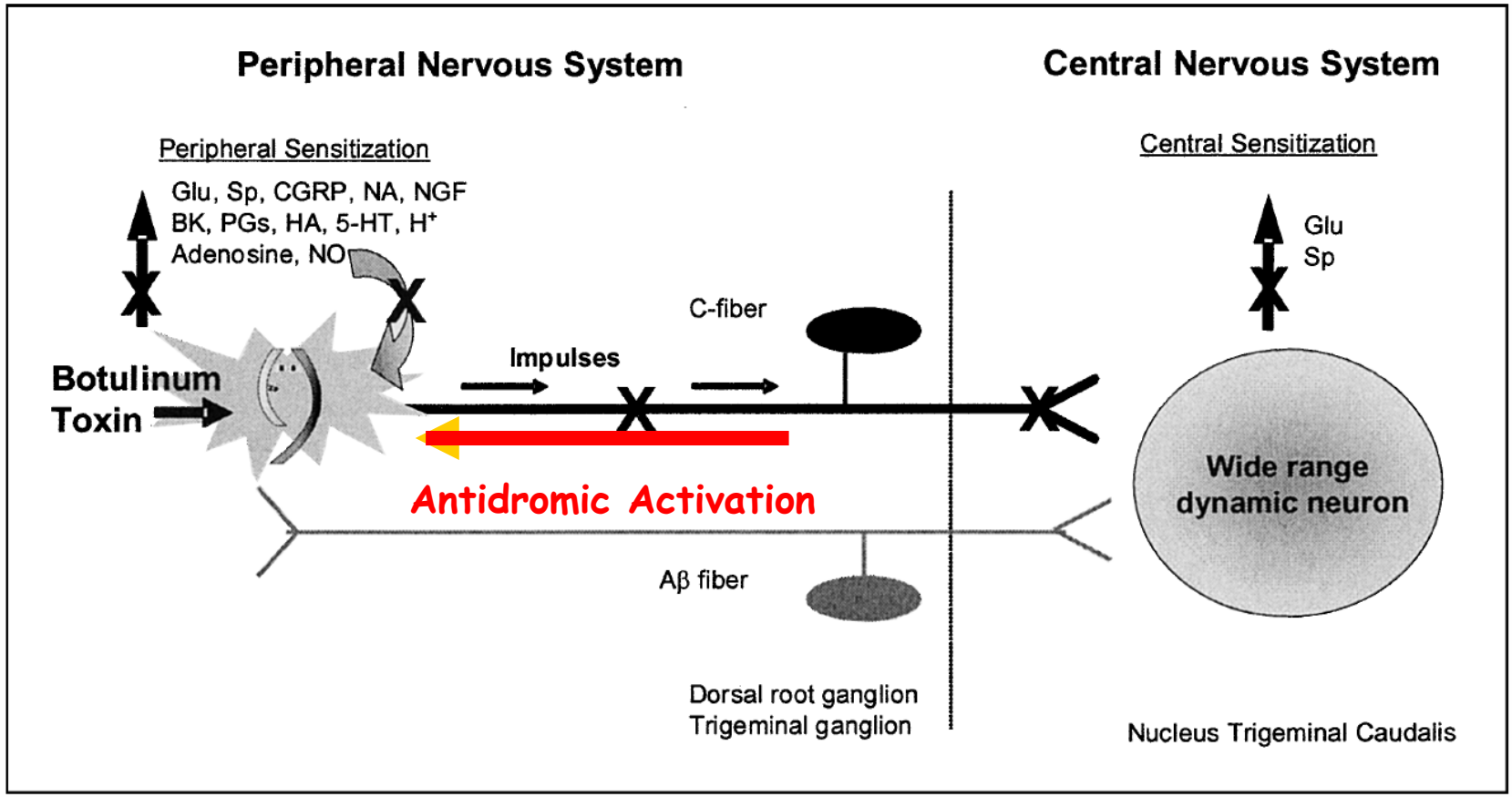
Conclusions From the PREEMPT Results

- PREEMPT, the largest clinical study of Chronic Migraine sufferers, demonstrated efficacy and tolerability of BOTOX®.
- BOTOX® was also effective in patients who overused acute medications and who were considered treatment refractory during the 28-day baseline period.
- Significant differences favoring BoNTA over placebo in the DB phase were observed at multiple visits for all efficacy endpoints evaluated in the OL phase, suggesting continued improvement with long-term BoNTA.

Reduction of Neurotransmission and Neurogenic Inflammation



Effect of BoNT on peripheral and central sensitization



Headache 2003;43[suppl 1]:S9-S15

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, Psy. D

-59 CM

-TPM(100-200)+ placebo injections (n = 30) vs. onabotulinumtoxinA injections (Fix:100u+F/U100u)+ placebo tablets (n = 29)

-12 weeks treatment

-both treatment were effectively, although the results were statistically significant within groups (headache days:-8.1 vs -8.0) but not between groups.

-BTX users had fewer adverse events.

Other treatment Options

- Gabapentin, pregabalin, tizanidine, fluoxetine, zonisamide, and memantine may be alternative or additive treatment options, but studies regarding these compounds still are underpowered and compelling data are missing.

Conclusion

- CM is a common headache disorder and presents a clinical treatment challenge.
- Only TPM and local injection of botulism toxin have been shown to be effective in placebo-controlled randomized trials for prophylaxis of CM with or without medication overuse.
- It may not be necessary to withdraw patients with CM from medication overuse before a treatment attempt with TPM or local injection of botulism.
- Reductions in migraine attack frequency may reduce the risk of developing CM.