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.
### Prevalence of Migraine Globally

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>5-12%</td>
</tr>
<tr>
<td>Denmark</td>
<td>10%</td>
</tr>
<tr>
<td>Germany</td>
<td>11%</td>
</tr>
<tr>
<td>Italy</td>
<td>12%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>9.1%</td>
</tr>
<tr>
<td>UK</td>
<td>7%</td>
</tr>
<tr>
<td>USA</td>
<td>9-12%</td>
</tr>
</tbody>
</table>

Adapted from Lipton RB, et al. *Headache*. 1994
Prevalence of Chronic Migraine Globally

USA: 1.3%
Brazil: 1.3%
Spain: 2.4%
Taiwan: 1.7%
Georgia: 1.4%
“Chronic”

In TACs (cluster, paroxysmal hemicrania, SUNCT)

Unremitting for \( \geq 1 \) years or
remission period \(< 1 \) month

In other headache disorders

On \( \geq 15 \) days/month and for \( \geq 3 \) months
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)

\[ \geq 15 \text{ days/month} \]
\[ \geq 3 \text{ months} \]
\[ \geq 4 \text{ hours per day} \]

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
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)

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

ICHD-II revised criteria for CM & MOH (ICHD-II<sub>R</sub>, 2006)

<table>
<thead>
<tr>
<th>Classification and source</th>
<th>Description and/or diagnostic criteria</th>
<th>Limitations of proposed criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transformed migraine</td>
<td>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</td>
<td>Easily applied in general practice but lacked the reliability to support academic and epidemiological studies of disease state and progression</td>
</tr>
<tr>
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<td>Limitations of proposed criteria</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Transformed migraine</td>
<td>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.</td>
<td>Limited in general practice by a dependence on a patient’s recall of their headache transformation.</td>
</tr>
<tr>
<td>Silberstein and Lipton Criteria, 1994</td>
<td>A. History of episodic migraine meeting any IHS criteria 1.1 to 1.6 B. Daily or almost daily (≥15 days/month) head pain for &gt;1 month C. Average headache duration of &gt;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</td>
<td></td>
</tr>
<tr>
<td>Classification and source</td>
<td>Description and/or diagnostic criteria</td>
<td>Limitations of proposed criteria</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td><em>Transformed migraine</em></td>
<td>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 (&gt;15 days/month) head pain for &gt;1 month. B. Average headache duration of &gt;4 hours day (if untreated). C. At least 1 of the following: 1. History of episodic migraine meeting any IHS criteria 1.1 to 1.5 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.</td>
<td>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.</td>
</tr>
<tr>
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<td>Limitations of proposed criteria</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>Migraine with an unfavorable evolution without typical symptom-free intervals between attacks</td>
<td></td>
</tr>
</tbody>
</table>
| Manzoni et al, 1995       | 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 |
<table>
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</tr>
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</table>
| 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 |
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</tr>
</thead>
</table>
| 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 ...

transformation

EM
CM

Part III

Risk factors of chronification and pathophysiology of CM
“Transform”

Episodic Migraine

? 

Chronic Migraine

?
# AMPP study

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chronic migraine</th>
<th>Episodic migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>47.7 (14.0)</td>
<td>46.0 (13.8)</td>
</tr>
<tr>
<td>Race, %</td>
<td>78.6</td>
<td>80.0</td>
</tr>
<tr>
<td>Employment</td>
<td>1 in 5 reported being “occupationally disabled”</td>
<td>1 in 10 reported being “occupationally disabled”</td>
</tr>
<tr>
<td>Household income, %</td>
<td>29.9%</td>
<td>24.9%</td>
</tr>
<tr>
<td>Mean BMI, n (SD)</td>
<td>29.8 (8.3)</td>
<td>29.2 (7.9)</td>
</tr>
<tr>
<td>Cutaneous allodynia, %</td>
<td>68.2</td>
<td>63.2</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td>More likely to report or meet criteria for psychiatric, pain, respiratory, and cardiovascular comorbid conditions</td>
<td>Less likely to report or meet criteria for psychiatric, pain, respiratory, and cardiovascular comorbid conditions</td>
</tr>
</tbody>
</table>
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.

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 alldynia.

“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

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.

Obesity

- Overweight individuals (BMI: 25–29) have a threefold higher risk of developing CM.
- Obesity (BMI > 30), has 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.

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.

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

Topiramate in the treatment of chronic migraine

M Silvestrini\textsuperscript{1,2}, M Bartolini\textsuperscript{1}, M Coccia\textsuperscript{1}, R Baruffaldi\textsuperscript{1}, R Taffi\textsuperscript{1} & L Provinciali\textsuperscript{1}

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

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,* Cetello 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 Diener¹, G Bussone², JC Van Oene³, M Lahaye³, S Schwalen³ & PJ Goadsby⁴,⁵ on behalf of the TOPMAT-MIG-201(TOP-CHROME) Study Group⁶

¹Department of Neurology, University of Duisburg-Essen, Germany, ²Department of Neurology, C. Besta' Neurological Institute, Milan, Italy, ³Janssen-Cilag EMEA, Tilburg, the Netherlands and Neuss, Germany, ⁴Institute of Neurology, London, UK and ⁵Department 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).
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%).
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.
Comprehensive Mechanisms

H₂CO₃ ⇋ H₂O + CO₂

Inhibition of carbonic anhydrase

Potentiation of GABA

Na⁺ and Ca²⁺ channel blockade

Antagonism of glutamate

GABA, receptor

Cl⁻ inhibition flux

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


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).

Inhibition of CSD after chronic treatment with migraine prophylactic drugs
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.
### Table: Botulinum neurotoxin (BoNT) for autonomic disorders and pain

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Class</th>
<th>Outcome measures</th>
<th>Adverse events</th>
<th>Conclusions</th>
<th>Recommendations*</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary hyperhidrosis</td>
<td>2</td>
<td>Gravimetry, responder rate; patient satisfaction</td>
<td>No difference between BoNT and placebo</td>
<td>Safe and effective</td>
<td>A</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>Palmar hyperhidrosis</td>
<td>2</td>
<td>Gravimetry, ninhydrin test; VAS</td>
<td>Injection pain, mild hand muscle weakness</td>
<td>Probably effective</td>
<td>B</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>Gustatory sweating</td>
<td>5</td>
<td>Area of sweating, ninhydrin test; self assessment</td>
<td>Injection pain</td>
<td>Possibly effective</td>
<td>C</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>Drooling</td>
<td>4</td>
<td>Drooling scores; weight of dental Isles; VAS</td>
<td>Dry mouth</td>
<td>Possibly effective</td>
<td>B</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>Detrusor overactivity</td>
<td>2</td>
<td>Urodynamic measures, QOL; frequency of incontinence</td>
<td>Urinary retention</td>
<td>Safe and effective</td>
<td>A</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>DSD in spinal cord injury</td>
<td>2</td>
<td>PRUV</td>
<td>None known</td>
<td>Probably effective</td>
<td>B</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>Low back pain</td>
<td>1</td>
<td>VAS, Oswestry low back pain questionnaire</td>
<td>None known</td>
<td>Possibly effective</td>
<td>C</td>
<td>Diverse etiologies for low back pain</td>
</tr>
</tbody>
</table>

**Episodic migraine**
- 2 Class II
- Change in frequency per month; proportion with 50% decrease in frequency compared with baseline
- Ptsis, local transient pain at the site of injection, bruising, cold sensation
- Probably ineffective
- 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 tautness, ptds, fulk-like reaction
- Probably ineffective
- Suboptimal dose and muscle selection may account for treatment failures

**Chronic daily headache**
- 4 Class II
- Change in headache-free days
- Ptsis, transient weakness of neck, fulk-like reaction
- Insufficient evidence
- 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
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

**Double-Blind Phase**
- Baseline: -4
- Randomization: Day 0
- Weeks: 4, 8, 12, 16, 20
- Primary Time Point: 24, 28, 32, 36, 40, 44, 48, 52, 56
- B: BoNT A
- P: Placebo

**Open-Label Phase**
- Treatment
- Phone interview

**Legend**
- 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 (≥80) 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

<table>
<thead>
<tr>
<th>Order</th>
<th>Muscle</th>
<th>Fixed-Site, Fixed-Dose (U)</th>
<th>Follow-the-Pain (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Corrugator</td>
<td>20 (5 each site)</td>
<td>NA</td>
</tr>
<tr>
<td>B</td>
<td>Procerus</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>C</td>
<td>Frontalis</td>
<td>20 (10 each site)</td>
<td>NA</td>
</tr>
<tr>
<td>D</td>
<td>Temporalis</td>
<td>40 (20 each site)</td>
<td>10 (up to 2 sites)</td>
</tr>
<tr>
<td>E</td>
<td>Occipitalis</td>
<td>30 (15 each side)</td>
<td>10 (up to 2 sites)</td>
</tr>
<tr>
<td>F</td>
<td>Cervical paraspinal</td>
<td>20 (10 each site)</td>
<td>NA</td>
</tr>
<tr>
<td>G</td>
<td>Trapezius</td>
<td>30 (15 each side)</td>
<td>20 (up to 4 sites)</td>
</tr>
</tbody>
</table>

Total number of units (U) = 155 to 195

NA = no additional
## Pooled Data: Baseline Demographics

2/3 previous prophylaxis failure
2/3 with MOH

### Baseline Patient Demographics and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>BOTOX° (n=688)</th>
<th>Placebo (n=696)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>41.1</td>
<td>41.5</td>
</tr>
<tr>
<td>Mean years since onset of Chronic Migraine</td>
<td>19.4</td>
<td>19.0</td>
</tr>
<tr>
<td>Female, %</td>
<td>87.6</td>
<td>85.2</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>89.7</td>
<td>90.5</td>
</tr>
<tr>
<td>Mean HA days during baseline</td>
<td>19.9</td>
<td>19.8</td>
</tr>
<tr>
<td>Mean migraine days during baseline*</td>
<td>19.1</td>
<td>18.9</td>
</tr>
<tr>
<td>Mean moderate/severe HA days during baseline</td>
<td>18.1</td>
<td>18.0</td>
</tr>
<tr>
<td>Mean cumulative hours of HA occurring on HA days during baseline</td>
<td>295.93</td>
<td>281.22</td>
</tr>
<tr>
<td>% Patients with severe (≥260) HIT-6 score during baseline†</td>
<td>93.5</td>
<td>92.7</td>
</tr>
<tr>
<td>Mean HA episodes during baseline</td>
<td>12.2</td>
<td>13.0</td>
</tr>
<tr>
<td>Mean migraine episodes during baseline*</td>
<td>11.4</td>
<td>12.2</td>
</tr>
<tr>
<td>% Patients who had previously used 1 or more HA preventive medications</td>
<td>61.8</td>
<td>65.2</td>
</tr>
<tr>
<td>% Patients overusing acute medications during baseline‡</td>
<td>64.8</td>
<td>66.1</td>
</tr>
<tr>
<td>Mean HIT-6 score during baseline†</td>
<td>65.5</td>
<td>65.4</td>
</tr>
</tbody>
</table>
# Pooled Data: Primary and Secondary Endpoints at Week 24

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

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

*HA = headache; HIT = Headache Impact Test
\(^\d\)P-values are from analyses of covariance (ANCOVA) with baseline as covariate. The main effects are treatment and medication overuse stratification.
\(^\d\)ICHD-II: 1.1 (migraine without aura); 1.2 (migraine with aura); 3.0 (probable migraine).
\(^\d\)Scores of 0-48 indicate little or no impact; 49-55, some impact; 56-59, substantial impact; 60+, severe impact.
\(^\d\)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

- **Double-blind phase**
  - BOTOX® vs placebo
  - BOTOX® (n=688)
  - Placebo (n=696)

- **Open-label phase**
  - All patients on BOTOX®

- **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

*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)
# Discontinuation Rates and Treatment-Related Adverse Events

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

<table>
<thead>
<tr>
<th>BOTOX\textsuperscript{®} (n=687)</th>
<th>Placebo (n=692)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.8%</strong></td>
<td><strong>1.2%</strong></td>
</tr>
</tbody>
</table>

Treatment-related AEs reported in $\geq 2\%$ of patients pooled data, double-blind phase\textsuperscript{1} (%)

<table>
<thead>
<tr>
<th>AEs</th>
<th>BOTOX\textsuperscript{®}</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck pain</td>
<td>6.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>3.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>3.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>2.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>3.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Headache</td>
<td>2.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>1.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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

Biochemical  Neurotransmitter Inhibited  Clinical Benefit

Cleavage of SNAP$_{25}$

Neuropeptides (SP, CGRP, etc) in C-afferent fibers

Reduction of Neurogenic Inflammation

ACh in motor nerves

Muscle Relaxation
Effect of BoNT on peripheral and central sensitization

Peripheral Nervous System
- Botulinum Toxin
- Peripheral Sensitization: Glu, Sp, CGRP, NA, NGF, BK, PGs, HA, 5-HT, H+, Adenosine, NO
- Antidromic Activation
- C-fiber
- Aβ fiber
- Dorsal root ganglion
- Trigeminal ganglion

Central Nervous System
- Central Sensitization
- Glu, Sp
- Wide range dynamic neuron
- Nucleus Trigeminal Caudalis

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.