Chronic Migraine: Diagnostic Challenges and Prophylactic Management

Astrid Gendolla
Essen
Germany
Currently, there are \(~2 \% \text{ of the population}\)*, mostly women, suffering from Chronic Migraine\textsuperscript{1}

However, only approximately 20\% of these patients receive a Chronic Migraine diagnosis\textsuperscript{2}

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\*Estimated global Chronic Migraine prevalence rate of 1 per cent as sourced from Natoli JL et al. Global Prevalence of Chronic Migraine: A Systematic Review. Cephalalgia. 2010 May;30(5):599-609 has been applied to 2010 CDN population figures for those 18+ years of age (n=27,196,554) (Source: Statistics Canada).

\textsuperscript{1} Natoli JL et al. Cephalalgia. 2010;30:599-609.

\textsuperscript{2} Bigal ME et al. Neurology. 2008;71:559-566.
Percentage of Patients which fulfill Diagnosis of CM / diagnosis through subspecialty
Primary headache disorders: classification\textsuperscript{1,2}

1. After secondary causes are ruled out

2. Primary headache disorders

- Chronic headache
  - Frequency \(\geq 15\) days/month

- Episodic headache
  - Frequency \(< 15\) days/month

- Short-duration chronic daily headache
  - Duration \(< 4\) hours or multiple discrete episodes

- Long duration chronic daily headache
  - Daily or near-daily headache lasting \(\geq 4\) hours

With or without medication overuse

Defining migraine features\textsuperscript{1,2}

- Unilateral
- Pulsating quality
- Moderate severe pain
- Aggravated by physical activity \(\geq 2 \text{ of these features}\)

- Nausea and/or vomiting
- Photophobia and phonophobia \(\geq 1 \text{ of these features}\)

- Treated and relieved with triptans or ergotamine- worsening with physical activity \(OR\)

Chronic Migraine: classification and diagnosis

ICHDI-2R ± Medication Overuse Combined Criteria

- Headache on ≥15 days per month for 3 months
- ≥5 prior migraine attacks
- On ≥8 days per month, headache fulfills criteria for migraine
  - Has ≥2 of the following:
    a) unilateral
    b) throbbing
    c) moderate or severe
    d) aggravated by physical activity
  AND
  - ≥1 of the following:
    a) nausea and/or vomiting
    b) photophobia and phonophobia
  OR
  - Treated and relieved with triptans or ergotamine

- Not attributed to another causative disorder
- Subclassified as w/ or w/out medication overuse

Simplified diagnosis

Diagnose chronic headache syndrome

Diagnosis migraine

With or without medication overuse

*GMAP recommendation
Neck symptoms are common during a migraine attack

75% of patients reported neck pain associated with migraine attacks

- Unilateral pain: 57%
- Throbbing: 5%
- Stiffness: 17%
- Tightness: 69%

Proportion reporting specific neck symptoms (%)
(N=144)

Chronic Migraine - Principles of treatment

• Exact diagnosis \(^1\)
• Identify/ minimize/ eradicate cofounding factors or triggers \(^1,2\)
• Identify and treat concomitant diseases or relevant factors which might influence outcome
• Exact anamnesis of current medication \(^2\)
• Design a treatment plan \(^1,2\)
  – Non medication Nicht-medikamentös
  – Acute and prophylactic treatment / frame for acute treatment
• Realize and monitor headache related disability \(^3\)

Treatment options for chronic migraine

- **Non pharmacological:**
  - behavioural therapy
  - Alternative therapies
  - Surgical therapies

Pharmacological

Acute

Prophylactic

Stratify treatment:
- Severity and frequency of migraine attacks
- Patient history
- Treatment of comorbidities

Migraine prophylaxis

**Aims**

- Reduce frequency, intensity and duration of migraine attacks
- Avoid progression of the disease
- Improve efficacy of acute treatment
- Reduce disability

**Side effects of the product**

**Risk of medication overuse**

**Choice of prophylactic substance**

**Compliance**

**Comorbidities**

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Grade of disability due to migraine

- Grade of disability is higher than other chronic diseases (diabetes, hypertension, coronary heart disease)

**Workplace/school**
- 74% of patients report reduction of productivity in the last 6 months

**Relationships**
- 62% of patients report loss of time with friends and family in the last 6 months

**Leisure activities**
- 67% of patients report not being able to adequately enjoy leisure activities
- 56% report social withdrawal

**Emotional well being**
- 86% of patients believe their life would be better if they had no migraine
- 34% fear migraine will be ruining their ability to enjoy good things in life

Quelle: ¹ S. Evers, Migräne – Fakten; Georg Thieme Verlag KG, ISN 3-13-143631-X
The burden of migraine – intra- and interindividual aspects

**Patient**
- Reduced quality of life
- Isolation
- Fear- ability to make plans, both in private and work life
- Side effects of medication

**Society**
- $\approx 3.6$ Milliarden Euro costs in Germany/year $^1$
- $\approx 1.5$ Milliarden Euro due to work abseintism $^1$
- $\approx 1.1$ Milliarden Euro due to reduced productivity $^1$
- $\approx 1.0$ Milliarden cost for therapy and medication $^1$

1 Quelle: Migräne Liga e.V. Deutschland
Structures involved in the pathophysiology of migraine\textsuperscript{1,2}

Chronic Migraine: key questions to determine *frequency*

1. **How many days per month do you have headache?**
   - Patients should experience ≥15 headache days per month\(^1\)

2. **How many days per month are you headache free?**
   - Patients may only report moderate to severe headache days\(^1\)

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1. Headache Classification Committee; Olesen J et al. Cephalalgia. 2006;26:742-746
Chronic Migraine: key questions to determine *migraine features*

- How many days per month do you have migraine?
- What headache features do you have?

At least 8 headache days per month should be classified as migraine days\(^1\)

Discuss migraine symptoms\(^2\):
- Unilateral
- Pulsating quality
- Moderate severe pain
- Aggravated by physical activity
- Nausea and/or vomiting
- Photophobia/phonophobia
- Treated or relieved with triptans or ergotamine

However, consider asking this differently...

- Use your hands to show me where your headache is?
- Is your preference to be in a dark room?
- Is your preference to be in a quiet area?
- Is your preference to be still?

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BOTOX® in Chronic Migraine: From Concept to Clinical Study

1st MEDLINE citations: “Botulinum & Wrinkles & Double-Blind” (Keen M)¹

“Botulinum & HA” (Zwart JA)²

Allergan Early Phase II investigation studies begin (Binder W)³

1st MEDLINE citation: “Botulinum & HA & Double-Blind” (Relja MA)⁴

BoNT-A as a migraine preventative treatment: Open-label study (Binder WJ)⁵

Double-blind study (Silberstein S)⁶

1994

1998

1999

2000

2001

2005

2009

2010

2011

Allergan Late Phase II investigation studies begin

Late Phase II development studies in CDH (Mathew NT, Dodick DW)⁷,⁸

PREEMPT Phase III study published⁹

First licence approval – BOTOX® in chronic migraine (UK)¹⁰

PREEMPT Phase III 56-week study published¹¹

Suppressive effects of botulinum toxin type A on the trigeminal/cervical nociceptive system activated by injection of capsaicin to forehead

- Botulinum toxin type A significantly reduced the capsaicin-induced pain intensity area ($p=0.011$).
- The suppressive effect of botulinum toxin type A in pain reduction was observed as early as first week.
- Mean area of secondary hyperalgesia was significantly smaller in botulinum toxin type A group than in saline group ($p=0.040$).
- These effects may be caused by a local peripheral effect of botulinum toxin type A on cutaneous nociceptors.

PREEMPT: Study design of two phase 3 studies of chronic migraine patients

- Largest clinical program on Chronic Migraine sufferers (1384 patients)
  - 122 sites in North America and Europe; 11 sites in Canada
  - 24-week randomized, double-blind, placebo-controlled phase and 32-week open-label phase

- Headache symptoms and medications were recorded in a daily telephone diary

## Pooled baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>Botulinum toxin type A (n=688)</th>
<th>Placebo (n=696)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Mean years since onset of CM</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Female, %</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Mean HA days (SD)</td>
<td>20 (4)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Mean migraine days (SD)</td>
<td>19 (4)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Mean moderate/severe HA days (SD)</td>
<td>18 (4.1)</td>
<td>18 (4.3)</td>
</tr>
<tr>
<td>Mean cumulative hours of HA occurring on HA days (SD)</td>
<td>296 (117)*</td>
<td>281 (115)*</td>
</tr>
<tr>
<td>Mean HIT-6 score</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>% Patients with severe (≥ 60) HIT-6 score</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>Mean HA episodes (SD)</td>
<td>12 (5)*</td>
<td>13 (6)*</td>
</tr>
<tr>
<td>Mean migraine episodes (SD)</td>
<td>11 (5)*</td>
<td>12 (5)*</td>
</tr>
<tr>
<td>% Patients overusing acute HA pain medication</td>
<td>65</td>
<td>66</td>
</tr>
</tbody>
</table>

HA = headache; HIT = Headache Impact Test. *p<0.05.

PREEMPT pooled analysis: Change in headache days – primary endpoint

~70% of patients* achieved ≥50% reduction in headache days at 56 weeks

*Patients who received botulinum toxin type A throughout the 56-week treatment program. Mean ± standard error.

The double-blind phase included 688 subjects in the botulinum toxin type A group and 696 in the placebo group. Headache days at baseline: 19.9 botulinum toxin type A group vs 19.8 placebo group, p=0.498.

PREEMPT Pooled Analysis: Mean Change from Baseline in Headache Days (primary)

• red line graph represents 100 u dosing, blue line graph 155 u -195 u

• Mean ± standard error.

• Aurora SK et al. Presented at IHC 2009.
PREEMPT: botulinum toxin type A is a well-tolerated treatment for chronic migraine

- No new treatment-related AEs were identified
- Most AEs were mild or moderate in severity and resolved without sequelae

<table>
<thead>
<tr>
<th>AE</th>
<th>botulinum toxin type A (n = 687)</th>
<th>Placebo (n = 692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck pain</td>
<td>60 (8.7)</td>
<td>19 (2.7)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (5.5)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (4.7)</td>
<td>22 (3.2)</td>
</tr>
<tr>
<td>Migraine</td>
<td>26 (3.8)</td>
<td>18 (2.6)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (3.6)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (3.6)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>23 (3.3)</td>
<td>14 (2.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3.1)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (2.6)</td>
<td>10 (1.4)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>15 (2.2)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Data on file. Allergan, Inc.
BOTOX® Reconstitution and Dilution

<table>
<thead>
<tr>
<th>Dilution Recommendation</th>
<th>Resulting BOTOX® dose (U per 0.1 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline added (0.9% sodium chloride injection)</td>
<td></td>
</tr>
<tr>
<td><strong>100 U vial</strong></td>
<td></td>
</tr>
<tr>
<td>2.0 mL</td>
<td>5.0 U</td>
</tr>
<tr>
<td><strong>200 U vials</strong></td>
<td></td>
</tr>
<tr>
<td>4.0 mL</td>
<td>5.0 U</td>
</tr>
</tbody>
</table>

- Resulting concentration is 5 U per 0.1 mL

Once reconstituted, BOTOX® must be injected or immediately stored at 2°C to 8°C.

BOTOX® Prescribing Information.
PREEMPT Injection sites

- The anatomic injection sites follow distributions and areas innervated by the trigeminal-occipital-cervical complex.

0.1 mL = 5 U/site.
Sensory nerves of the scalp

A. Corrugator
B. Procerus
C. Frontalis

Dosing for Chronic Migraine Using the PREEMPT Follow-the-Pain Injection Paradigm

<table>
<thead>
<tr>
<th>Order</th>
<th>Muscle</th>
<th>Number of Units (U)*</th>
<th>Additional Units (U), if necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Corrugator†</td>
<td>10 (5 each side)</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 side)</td>
<td>NA</td>
</tr>
<tr>
<td>D</td>
<td>Temporalis†</td>
<td>40 (20 each side)</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 side)</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>
<tr>
<td><strong>Total number of units (U)</strong></td>
<td><strong>155</strong></td>
<td><strong>to</strong></td>
<td><strong>195</strong></td>
</tr>
</tbody>
</table>

Dosing and results in these studies are specific to the formulation of BOTOX® manufactured by Allergan. The Allergan formulation is not interchangeable with other botulinum toxin products and cannot be converted using a dose ratio.

*Each IM injection site = 0.1 mL = 5 U BOTOX.
†Dose distributed bilaterally for the minimum 155 U dosing.

NA = no additional

Injection Sites for The Procerus, Corrugator and Frontalis Muscles

Injection Sites for the Temporalis Muscle

Injection Sites for the Occipitalis, Cervical Paraspinal and Trapezius Muscles