Role of Botulinum toxin for chronic migraine treatment

肉毒桿菌於慢性偏頭痛的治療

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Agenda

- Overview of chronic migraine
- Clinical data on botulinum toxin in patients with headache disorders
- Mechanism of action of BoNT/A in migraine
- My Personal experience
Chronic daily headache (CDH)

- CDH is a syndrome, not a diagnosis
- Daily or near-daily headache (≥15 days/month; ≥3 months)
- The most frequent headache type in headache clinics (60%).
- Frequently with medication-overuse headache (MOH)
Chronic daily headache (CDH)

- ICHD-II (2004): defined
  - Chronic (transformed) migraine (CM)
  - Chronic tension-type headache (CTTH)
  - New daily persistent headache (NDPH)
  - Hemicrania continua (HC)
  - Medication overuse headache (MOH)

- ICHD-II revised criteria for CM & MOH (ICHD-II\textsubscript{R}, 2006)
ICHD-II\textsubscript{R} criteria for chronic migraine (CM)

A. Headache (TTH or migraine): \(\geq 15\) days/month for \(\geq 3\) months

B. has had \(\geq 5\) attacks of Migraine without aura

C. Headache \(\geq 8\) days/month for \(>3\) months, fulfilling C1 or C2:
   - C1. fulfilling the criteria C & D of migraine without aura
   - C2. Relieved by triptan or ergot, before C1 above

D. No medication overuse and not attributed to another causative disorder
Chronic Migraine

- **Epidemiology**
  - 2.4% general population experience CM and that 30-50% of those overuse headache medication.
  - Chronic Migraine (CM) represents ~ 90% of the cases of chronic daily headache seen in a headache specialty clinic.

- **Annual Incidence**
  - 14% among patients with Episodic Migraine developed Chronic Migraine
  - age (>51 y/o, vs. <34 y/o, OR=4.4)
  - Headache frequency (10-15 d/m, vs 0-4 d/m, OR=25.4)
  - Medication overuse (OR=23.4)

1 Castillo et al. Headache 1999
2 Bigal et al. Headache 2003
Pain 2003;106:81-9
## Psychiatric Comorbidity among CDH Subtypes

<table>
<thead>
<tr>
<th></th>
<th>CDH (n=261)</th>
<th>CM (n=152)</th>
<th>CTTH (n=92)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive disorders</td>
<td>66%</td>
<td>70%</td>
<td>59%</td>
<td>0.06</td>
</tr>
<tr>
<td>Any anxiety disorders</td>
<td>36%</td>
<td>43%*</td>
<td>25%*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Any depressive or anxiety disorder</td>
<td>73%</td>
<td>78%*</td>
<td>64%*</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Headache 2000;40:818-23
Management of Chronic Migraine

- Establish the correct diagnosis
- Reduce the aggravating factors
- Treat the comorbidity such as depression
- Limit acute headache treatment
- Put on migraine preventive agents
- Neuroimaging: not mandatory
- Withdraw medication overuse (detoxification) is the most important

Detoxification

- Outpatient clinic
  - Prednisone (60 mg for 2 days, 40 mg for 2 days, and 20 mg for 2 days) for 6 days or the combination of
  - tizanidine (slowly titration to 24mg over 4 weeks)
  - long-acting NSAID

- In-patient treatment
  - fail outpatient withdrawal
  - have a significant complicating medical indication, such as brittle diabetes mellitus
  - presence of psychiatric disturbances esp. MDD
Detoxification - In-patient treatment

- Novamin (prochlorperazine 5-10mg q8h, 63% headache free & >90% improvement)
  - Additional anti-histamine for EPS prevention
  - block the hunger for pain killer

- MgSO₄:
  - MgSO₄ 10 amp in NS 500ml iv pump for 24hr.

- Steroid
  - Methylprednisolone 100mg iv q12h(particularly if the rebound headache proves to be severe or if status migrainosus develops)

- Keto:
  - 1amp iv / im q8h for pain relief
## Commonly-Used Preventative Headache Medications

<table>
<thead>
<tr>
<th>Preventative (prophylactic)</th>
<th>Episodic Migraine</th>
<th>Chronic Migraine/CDH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studied</td>
<td>FDA Approval</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong>&lt;br&gt;(Topiramate*, divalproex sodium*, gabapentin†)</td>
<td>YES</td>
<td>YES*</td>
</tr>
<tr>
<td><strong>Antidepressants</strong>&lt;br&gt;(fluoxetine)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Beta Blockers</strong>&lt;br&gt;(Propranolol, timolol)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td><strong>Botulinum Toxins</strong>&lt;br&gt;(BOTOX®)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Ergot Derivatives</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>NSAID’s</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td><strong>α-2 Agonists</strong>&lt;br&gt;(Tizanidine)</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

*Studied in double-blind, placebo-controlled trials in chronic migraine and/or chronic daily headache

No medication is currently approved specifically for the prophylactic treatment of Chronic Migraine.
Studied Chronic Migraine / Chronic Daily Headache:
Cumulative number of CM / CDH patients studied

- BoNTA = BOTOX®: Allergan, Inc., Irvine, CA, USA
- Topamax®: Ortho-McNeil Inc., Titusville, NJ, USA
- Zanaflex®: Elan Inc., Dublin, Ireland
- Neurontin®: Pfizer Inc., New York, NY
- Prozac®: Eli Lilly Inc., Indianapolis, IN

CM = Chronic Migraine
CDH = Chronic Daily Headache
Clinical data on botulinum toxin in patients with headache disorders
Rationale for the use of BoNT/A in headache disorders

Strabismus, Blepharospasm, hemifacial spasm, dystonia...

cosmetic use

Headache/pain
Three methods of administration of BTX

- A fixed site approach
- Follow the Pain
- A combination approach
BoNTA Studies - Injection Paradigms

- Procerus
- Corrugators
- Temporalis
- Frontalis
- Occipitalis
- Semispinalis capitis
- Splenius capitis
- Trapezius
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

<table>
<thead>
<tr>
<th>Refs.</th>
<th>No. of patients</th>
<th>Dose [units]; distribution; formulation of BoNT/A</th>
<th>Rating of study (evidence class)</th>
<th>Result*</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rollnik et al. (2000)</td>
<td>21</td>
<td>200; FS; Dysport®</td>
<td>II</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Schmitt et al. (2001)</td>
<td>60</td>
<td>20; FS; Botox®</td>
<td>II</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Pacberg et al. (2004)</td>
<td>40</td>
<td>100; FTP; Botox®</td>
<td>I</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Schulte-Mattler et al. (2004)</td>
<td>112</td>
<td>500; FS; Dysport®</td>
<td>I</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Silberstein et al. (2005)</td>
<td>300</td>
<td>50, 85, 100, 150; FS; Botox®</td>
<td>I</td>
<td>–</td>
<td>0</td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication to treatment</th>
<th>Patients, n</th>
<th>Results compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Göbel et al. (1999) [8]</td>
<td>Chronic tension-type headache</td>
<td>10</td>
<td>No significant reduction of pain intensity, headache hours, or use of analgesics</td>
</tr>
<tr>
<td>Snuits et al. (1999) [9]</td>
<td>Chronic tension-type headache</td>
<td>41</td>
<td>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</td>
</tr>
<tr>
<td>RoInik et al. (2000) [10]</td>
<td>Chronic tension-type headache</td>
<td>21</td>
<td>No significant differences between botulinum toxin and placebo in any headache parameters</td>
</tr>
<tr>
<td>Burch et al. (2001) [11]</td>
<td>Episodic and chronic tension-type headache</td>
<td>41</td>
<td>No significant difference in headache frequency</td>
</tr>
<tr>
<td>Schmitt et al. (2001) [12]</td>
<td>Chronic tension-type headache</td>
<td>59</td>
<td>No significant differences between botulinum toxin and placebo in any headache parameters</td>
</tr>
<tr>
<td>Kokoska et al. (2004) [14]</td>
<td>Chronic tension-type headache</td>
<td>40</td>
<td>No significant reduction of headache frequency; significant reduction of pain intensity</td>
</tr>
<tr>
<td>Padberg et al. (2004) [15]</td>
<td>Chronic tension-type headache</td>
<td>40</td>
<td>No significant results</td>
</tr>
<tr>
<td>Empl et al. (2005) [16]</td>
<td>Chronic tension-type headache</td>
<td>125</td>
<td>No significant results</td>
</tr>
<tr>
<td>Silberstein et al. (2006) [17]</td>
<td>Chronic tension-type headache</td>
<td>300</td>
<td>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</td>
</tr>
</tbody>
</table>
Clinical data on botulinum toxin in patients with episodic migraine

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

*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.
Botulinum Toxin Type A as a Migraine Preventive Treatment

*Headache 2000;40:445-450*

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 ≤ .042).
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication to treatment</th>
<th>Patients, n</th>
<th>Results compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondo et al. (2004) [41]</td>
<td>Chronic daily headache</td>
<td>50</td>
<td>No significant reduction but trend ((P = 0.07)) in primary endpoint (days with headache)</td>
</tr>
<tr>
<td>Silberstein et al. (2005) [42*]</td>
<td>Chronic daily headache</td>
<td>792</td>
<td>No significant reduction of headache frequency</td>
</tr>
<tr>
<td>Mathew et al. (2005) [43*]</td>
<td>Chronic daily headache</td>
<td>355</td>
<td>Primary endpoint (reduction of headache-free days) negative; secondary endpoint (percentage of patients with reduction &gt; 50%) positive</td>
</tr>
<tr>
<td>Dodick et al. (2005) [44*]</td>
<td>Chronic daily headache</td>
<td>228</td>
<td>Significant reduction of headache frequency in patients not receiving other prophylactic drugs (subanalysis of study [43*])</td>
</tr>
<tr>
<td>Elkind and Turkel (2005) [45]</td>
<td>Chronic migraine</td>
<td>355</td>
<td>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*])</td>
</tr>
</tbody>
</table>
2005, Mathew & Silberstein et al. - Study Design

Baseline → Placebo

Placebo Non-Responder (PNR)

BoNT A* → Placebo

BoNT A* → Placebo

BoNT A* → Placebo

BoNT A* → Placebo

Primary analysis

Final analysis

-60 -30 0 Day 90 180 270
Research Submission

Botulinum Toxin Type A (BOTOX®) for the Prophylactic Treatment of Chronic Daily Headache: A Randomized, Double-Blind, Placebo-Controlled Trial
- Prior medication including prophylactic agents were allowed throughout the study
- 36% on prophylactic agents
- 47% medication overuse

- Follow-the-pain approach

<table>
<thead>
<tr>
<th>Muscle Injected (Allowable Dose Range)</th>
<th>Treatment Cycle 2 (Day 0)</th>
<th>Treatment Cycle 3 (Day 90)</th>
<th>Treatment Cycle 4 (Day 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal/glabellar (25 to 40 U)</td>
<td>38.0 U (40 U)</td>
<td>37.3 U (40 U)</td>
<td>37.1 U (40 U)</td>
</tr>
<tr>
<td>Occipitalis (20 U)</td>
<td>19.8 U (20 U)</td>
<td>19.8 U (20 U)</td>
<td>19.7 U (20 U)</td>
</tr>
<tr>
<td>Temporalis (20 to 50 U)</td>
<td>42.0 U (40 U)</td>
<td>42.7 U (45 U)</td>
<td>43.7 U (40 U)</td>
</tr>
<tr>
<td>Masseter (optional; 0 to 50 U)</td>
<td>8.0 U (0 U)</td>
<td>7.6 U (0 U)</td>
<td>6.5 U (0 U)</td>
</tr>
<tr>
<td>Trapezius (20 to 60 U)</td>
<td>47.4 U (60 U)</td>
<td>48.3 U (60 U)</td>
<td>48.4 U (60 U)</td>
</tr>
<tr>
<td>Semispinalis (10 to 20 U)</td>
<td>18.2 U (20 U)</td>
<td>18.0 U (20 U)</td>
<td>17.9 U (20 U)</td>
</tr>
<tr>
<td>Splenius capitis (10 to 20 U)</td>
<td>18.6 U (20 U)</td>
<td>18.1 U (20 U)</td>
<td>18.1 U (20 U)</td>
</tr>
<tr>
<td>Total</td>
<td>190.8 U (200 U)</td>
<td>190.9 U (200 U)</td>
<td>190.5 U (200 U)</td>
</tr>
</tbody>
</table>
Primary efficacy measure - Mean Change in Headache-Free Days

Baseline: PNR BoNTA* = 5.8, PNR Placebo=5.5, pr BoNTA* =10.7, pr Placebo =9.9
% of Patients with $>$50% Decrease in Headache Days

(Placebo responders and placebo non-responders pooled)
% of Patients with ≥50% Decrease in Frequency of Headache Episodes

- BoNTA*: (n=173)
- Placebo: (n=182)

* p<0.05

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Adverse Events

Discontinuation due to adverse events: BoNTA* 2.3% and Placebo 0.5%

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event</th>
<th>BoNTA*</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck Pain</td>
<td>23 (13.3%)</td>
<td>1 (0.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arm Pain</td>
<td>7 (4%)</td>
<td>1 (0.5%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Injection Site Hemorrhage</td>
<td>2 (1.2%)</td>
<td>9 (4.9%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Muscular Weakness</td>
<td>38 (22%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin Tightness</td>
<td>8 (4.6%)</td>
<td>0 (0%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Blepharoptosis</td>
<td>12 (6.9%)</td>
<td>1 (0.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- No significant difference: Headache, neck rigidity, pain, face pain, dysphagia, hypertonia, hyperesthesia, dizziness, pharyngitis, visual disturbance
- Majority of AE's were mild to moderate in severity and transient in nature
Botulinum Toxin Type A for the Prophylaxis of Chronic Daily Headache: Subgroup Analysis of Patients Not Receiving Other Prophylactic Medications: A Randomized Double-Blind, Placebo-Controlled Study

- No Concomitant prophylaxis
- Mathew study: 355 patients enrolled
  \[228 \text{ (64\%)}\] were not taking concurrent prophylactic headache medication at time of enrollment (and during the trial)
- These 228 were pooled patients: both placebo non-responder(PNR) and placebo responder(pr)
Subgroup analysis in those without prophylaxis:

**Headache-free days**
10.0 vs 6.7 days, \( p=0.038 \)

**Headache frequency** ↓
Exploding vs. imploding headache

- Botulinum toxin works only in those with **imploding** and **ocular-type** headaches but not exploding headaches.

Rami Burstein et al. Pain. 2006;125:286-95
Research Submission

Predictors of Response to Botulinum Toxin Type A (BoNTA) in Chronic Daily Headache

- CM(71) response >> CTTH(11) 76.1% vs 36.4%
- CM
- Unilateral
- Pericranial tenderness
- Scalp allodynia
Botulinum Toxin Type A for the Treatment of Headache

Why We Say Yes

Ari Ashkenazi, MD; Stephen Silberstein, MD, FACP

Headache Therapy With Botulinum Toxin

Form Over Substance

Ann Pakainis, MD; James Couch, MD

Questioning Botulinum Toxin for Headache

Reality or Illusion

E. S. Roach, MD

Arch Neurol 2008 Jan, 65, 146-152
Possibly related factors so far ..

- Medication overuse (+, poor outcome)
- Disease duration (>30 years, poor outcome)
- Disease severity (headache free days, better)
- Headache characteristics (imploding+, better)
- Outcome measure (difference in headaches of moderate to severe intensity, >4 hrs in duration)

- Treatment related factors
  - Different dosage with different approaches
  - High placebo effect

Arch Neurol 2008 Jan, 65, 146-152
Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review) *Neurology* 2008;70:1707-1714

<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>Class I</td>
<td>Sarainmetry; 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>Class II</td>
<td>Sarainmetry; 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>Class III</td>
<td>Age 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>Class II</td>
<td>Drooling scores; weight of dental roles; VAS</td>
<td>Dry mouth</td>
<td>Probably effective</td>
<td>B</td>
<td>No head-to-head comparisons with other treatment options</td>
</tr>
<tr>
<td>Detrusor overactivity</td>
<td>Class II</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>Class II</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>Class II</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>
<tr>
<td>Episodic migraine</td>
<td>Class I and Class II</td>
<td>Change in frequency per month; proportion with 50% decrease in frequency compared with baseline</td>
<td>Progosis, local transient pain at the site of injection, bruising, diplopia</td>
<td>Probably ineffective</td>
<td>B</td>
<td>Suboptimal dose and muscle selection may account for treatment failures</td>
</tr>
<tr>
<td>Tension-type headache</td>
<td>Class I</td>
<td>VAS; area under the curve; proportion of severe headaches post treatment</td>
<td>Transient weakness of neck muscles; local skin tension; proptosis; fulike reaction</td>
<td>Probably ineffective</td>
<td>B</td>
<td>Suboptimal dose and muscle selection may account for treatment failures</td>
</tr>
<tr>
<td>Chronic daily headache</td>
<td>Class II</td>
<td>Change in headache-free days</td>
<td>Progosis, transient weakness of neck; fulike reaction</td>
<td>Insufficient evidence</td>
<td>U</td>
<td>Suboptimal dose and muscle selection may account for treatment failures</td>
</tr>
</tbody>
</table>
Chronic migraine clinical trial will be soon published!

GUIDELINES FOR CONTROLLED TRIALS OF PROPHYLACTIC TREATMENT OF CHRONIC MIGRAINE IN ADULTS

Taskforce of the International Headache Society Clinical Trials Subcommittee

Task force members:

Silberstein S (Chairman) (USA), Tfelt-Hansen P (Co-Chairman) (Denmark), Dodick DW (USA), Limmroth V (Germany), Lipton RB (USA), Pascual J (Spain), Wang SJ (Taiwan)
Proposed mechanism of action of BoNT-A in chronic migraine
## Botulinum Neurotoxins

<table>
<thead>
<tr>
<th></th>
<th>Neurotoxin Protein Complex Sizes (^1)</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>300 kD</td>
</tr>
<tr>
<td>B</td>
<td>300 kD</td>
</tr>
<tr>
<td>C(_1)</td>
<td>300 kD</td>
</tr>
<tr>
<td>D (HA+)</td>
<td>300 kD</td>
</tr>
<tr>
<td>E</td>
<td>300 kD</td>
</tr>
<tr>
<td>G</td>
<td>300 kD</td>
</tr>
</tbody>
</table>

\(^1\) Data from: [1]
Soluble *N*-ethylmaleimide sensitive factor attachment receptor (SNARE) protein
Cleavage Sites of BoNTs

Adopted from Breidenbach: TRENDS in Molecular Medicine Vol.11 No.8 August
Inhibiting Neurotransmitter Release

By BoNT/A
Mechanism of action of BoNT/A in pain/migraine

- Botulinum toxin type A was initially thought to provide pain relief by reducing muscle spasms.
- Even so, the reduction of pain often occurs before the decrease in muscle contractions suggesting that botulinum toxin type A has a more complex mechanism of action than initially hypothesized.
- Current data points to an antinociceptive effect of botulinum toxin type A that is separate from its neuromuscular activity.
Evidence for Antinociceptive Activity of Botulinum Toxin Type A in Pain Management

- Inhibit substance P release from embryonic dorsal root ganglion neurons in vitro (Welch et al., 2000)
- Inhibit CGRP release from trigeminal ganglion neurons in vitro (Durham and Cady, 2004)
- Inhibit glutamate release from peripheral nociceptors terminating in the dorsal horn in vivo (Cui et al., 2004)
- Reduction of c-fos gene expression in the dorsal horn of the spinal cord, and inhibited the excitation of wide dynamic range neurons of the dorsal horn (Aoki KR et al., 2005).
- In human study of trigeminal-related sensitization, significant suppressive effects of BoNT/A on capsacin induced pain and cutaneous allodynia were reported (Gazerani P et al., 2006, 2009).
Reduction of Neurotransmission and Neurogenic Inflammation

Biochemical

Neurotransmitter Inhibited

Clinical Benefit

Cleavage of SNAP$_{25}$

ACh in motor nerves

Muscle Relaxation

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

Peripheral

Reduction of Neurogenic Inflammation
Peripheral Sensitization Leads to Central Sensitization

Peripheral Stimulation → Antidromic Activation → Additional Activation → CNS → Release of Glutamate and Peptides in CNS

Peripheral Sensitization
- TRPV1 expression
- Increased afferent signals

Central Sensitization
- Inhibition at the dorsal horn
Personal experience

- My injection method is combined follow the pain with fixed side approach with larger dose.

- 9 cases were CM with medical refractory.
- 1M/8F
- Mean dose (100-150 units)
Fixed-Site-Fixed-Dose & Follow-the-Pain
Conclusion
適應症

- 眼瞼痙攣
- 半面痙攣
- 局部肌肉痙攣
- 斜視
- 痙攣性斜頸
- 小兒腦性麻痺引起之肌肉痙攣
- 皺眉紋
- 原發性腋窩多汗症
- 成人中風後之手臂痙攣
Off-label use

根据衛生署的解釋，藥品「仿單核准適應症外的使用」
原則如下：
一、需基於治療疾病的需要（正當理由）。
二、需符合醫學原理及臨床藥理（合理使用）。
三、應據實告知病人。
四、不得違反藥品使用當時，已知的、具公信力的醫學
文獻。
五、用藥應盡量以單方為主，如同時使用多種藥品，應
特別注意其綜合使用的療效、藥品交互作用或不良反應
等問題。

醫療法第81條規定：醫療機構診治病人時，應向病人或
其法定代理人、配偶、親屬或關係人告知其病情、治療
方針、處置、用藥、預後情形及可能之不良反應。
The recommended indications

- Those who demonstrate a lack of improvement from preventive Pharmacotherapy;
- Those who experience severe and intolerable adverse events from preventive medications;
- Those who refuse to use daily medications;

and elderly patients with **chronic** migraine.
Thank You for your attention