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Learning Objectives

At the conclusion of this workshop, participants will be better able to:

• Identify patients who are candidates for nerve stimulators or nerve blocks for management of headache
• Explain the benefits and risks of extracranial nerve blocks and Onabot A for the management of headache and chronic migraine (CM), respectively
• Acquire competency in performing:
  – Occipital nerve, supraorbital, supratrochlear, and auriculotemporal nerve blocks in appropriate patients with headache
  – OnabotA injections in patients with CM

Nerve Stimulation and Blocks

• New neurostimulators/neuromodulators
  – Spring TMS® Total Migraine System
  – Cefaly
• Stimulators
  – Extracranial
    – Occipital nerve
    – Supraorbital
    – Vagus nerve
    – Transtemporal transcranial magnetic stimulation
  – Intracranial
    – Sphenopalatine ganglion
    – Hypothalamic
• Nerve blocks—Practice Workshop
  – Occipital nerve, supraorbital, supratrochlear, auriculotemporal
Nerve Stimulation and Blocks

- **New neurostimulators/neuromodulators**
  - Spring TMS® Total Migraine System
  - Cefaly

- **Nerve Blocks**
  - Occipital nerve, supraorbital, supratrochlear, auriculotemporal
  - Hypothalamic

New Neurostimulators/Neuromodulators

- Spring TMS® Total Migraine System
  - Transcranial magnetic stimulation
  - For acute treatment of migraine with aura
  - Approved by the FDA

- Cefaly
  - Supraorbital nerve stimulation
  - For prevention of migraine
  - Approved by the FDA

New Neurostimulators/Neuromodulators

- Sphenopalatine ganglion stimulation
- Vagal nerve stimulation

For Acute Treatment of Cluster Headache

Slide courtesy of Andrew Charles, MD
Nerve Stimulation and Blocks

- New neurostimulators/neuromodulators
  - Spring TMS® Total Migraine System
  - Cefaly
- Stimulators
  - Extracranial
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- Nerve blocks—Practice Workshop
  - Occipital nerve, supraorbital, supratrochlear, auriculotemporal

Bilateral Extracranial Stimulation of the Greater Occipital Nerve for CM

Patients reported in literature
492

Combined response rate
56%
Randomized Placebo-Controlled Studies of Occipital Nerve Stimulation for CM

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Trial</th>
<th>Blinding</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONSTIM N=60</td>
<td>Preset stim 1 min/day Medical managed</td>
<td>None BUT intra-operative testing for adequate paresthesia coverage</td>
<td>Placebo group without remote</td>
<td>None</td>
</tr>
<tr>
<td>PRISMF N=139</td>
<td>1 s on / 90 s off</td>
<td>Yes; 5-10d active and placebo trial</td>
<td>Placebo group without remote</td>
<td>Migraine days/month at week 12</td>
</tr>
<tr>
<td>St Jude N=157</td>
<td>No stimulation</td>
<td>Yes; only those with &gt;50% pain relief enrolled</td>
<td>Placebo programmer used</td>
<td>Responder rate (&gt;50% ↓ VAS)</td>
</tr>
</tbody>
</table>


Occipital Nerve Stimulation May Restore Central Descending Opioidergic Tone...  
Progressive deactivation in pain matrix...except hypothalamus


But It Does Not Deactivate the Generator

Progressive deactivation in pain matrix...except hypothalamus

Explain:  
- Immediate pain when stimulation stops  
- Persistent autonomic symptoms

Magis et al. BMC Neurology. 2011;11:25
Occipital Nerve Stimulation for Trigeminal Autonomic Cephalalgias

<table>
<thead>
<tr>
<th>Headache Treated</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemizrania continua</td>
<td>&gt;80% response (n=6/8)</td>
</tr>
<tr>
<td>Chronic cluster</td>
<td>74% responder rate (n=39/53 experienced &gt;50% improvement)</td>
</tr>
<tr>
<td>SUNCT (n=5) and SUNA (n=1)</td>
<td>&gt;50% benefit (n=4 patients nearly pain-free)</td>
</tr>
</tbody>
</table>

*SUNCT, Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; SUNA, short-lasting unilateral neuralgiform headache attacks with autonomic symptoms.

Headache Treated Outcomes

- **Hemicrania continua**: >80% response (n=6/8)
- **Chronic cluster**: 74% responder rate (n=39/53 experienced >50% improvement)
- **SUNCT (n=5) and SUNA (n=1)**: >50% benefit (n=4 patients nearly pain-free)

Supraorbital Transcutaneous Stimulation Plus Occipital Nerve Stimulation

**Adults**
- 44/93 were responders
- Frequency of severe headaches decreased by 81% (19 to 3.6/month)
- 50% had near-complete relief
- MIDAS dropped by 84% (171 to 27)

**Adolescents, 13–17 years**
- 9/11 were responders
- 60% headache-free

Supraorbital Transcutaneous Stimulation for Prevention of Episodic Migraine

- Double-blind, randomized, sham-controlled trial (N = 67)
- Neurostimulation for 20 mins/day
- 250 us, 16 mA, 60 Hz
### Supraorbital Transcutaneous Stimulator: Safety and Patient Satisfaction

<table>
<thead>
<tr>
<th>AEs Reported by &gt;1 Patient (40-day trial period)</th>
<th>Patients (N)</th>
<th>AEs (%)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not like the feeling and want to discontinue use</td>
<td>29</td>
<td>29.29</td>
<td>1.25</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>12</td>
<td>12.12</td>
<td>0.52</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>12.12</td>
<td>0.52</td>
</tr>
<tr>
<td>Reversible forehead skin irritation</td>
<td>5</td>
<td>5.05</td>
<td>0.22</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>4.04</td>
<td>0.17</td>
</tr>
<tr>
<td>Feeling of fatigue</td>
<td>3</td>
<td>3.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Forehead paralysis for several minutes post-session</td>
<td>3</td>
<td>3.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Feeling of stress during the session</td>
<td>3</td>
<td>3.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Stiffness of shoulder</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Dental pain during the session or at the beginning</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Inability to keep eyes open during sessions</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
<tr>
<td>Feeling of confusion on the forehead during a few days</td>
<td>2</td>
<td>2.02</td>
<td>0.09</td>
</tr>
</tbody>
</table>

After 58.2 days on average, 46.6% of the 2,313 renters were not satisfied and returned the device.


### Allergic Skin Reactions to the Supraorbital Transcutaneous Stimulator

Transient local skin allergy was seen in 0.09% of patients (2/99).


### Vagal Nerve Stimulation

- Vagus nerve innervates multiple anatomical structures potentially involved in migraine
- Branches of cervical nerves innervating the dura may travel with the vagus nerve
- VNS reduces allodynia + glutamate release in response to inflammatory soup applied to dura in rats
- VNS with implanted stimulators effective for migraine and cluster headache

Effect of noninvasive vagus nerve stimulation on acute migraine: An open-label pilot study

P. J. Reschley, J. H. O'Neill, F. M. Hering, G. M. Kraft, and A. A. Weinstein

27 subjects, 80 attacks treated

<table>
<thead>
<tr>
<th>Baseline pain</th>
<th>Pain-free</th>
<th>Pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe</td>
<td>22</td>
<td>43</td>
</tr>
<tr>
<td>Mild</td>
<td>38</td>
<td>-</td>
</tr>
</tbody>
</table>

Relevant AEs: Neck twitching (1), Raspy voice (1)

Follow-up Studies: Noninvasive Vagal Nerve Stimulation for Prevention of Headache

EVENT Study Timeline

Patients
- 59 enrolled, 49 completed protocol
- At least 15 days of headache/month for previous 3 months

Treatments
- 3 per day
- 2 90-second administrations per treatment

Follow-up Studies: Noninvasive Vagal Nerve Stimulation for Prevention of Headache

Headache Days per 28 Days

- End of Run-in: 20.9 (nVNS), 22 (Sham)
- End of Comparative: 19 (nVNS), 22.2 (Sham)

Silberstein S et al, AHS 2014
Follow-up Studies: Noninvasive Vagal Nerve Stimulation for Prevention of Headache

Mean Change in Headache Days per 28 Days

*nP=0.1249

Silberstein S et al, AHS 2014

Follow-up Studies: Noninvasive Vagal Nerve Stimulation for Prevention of Headache

Responders to Treatment (%)

Silberstein S et al, AHS 2014

Transcranial Magnetic Stimulation

Image courtesy of Mayo Foundation for Medical Education and Research
Rationale:
Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation is now FDA-approved for treatment of medication refractory depression*

Transcranial magnetic stimulation can inhibit cortical spreading depression in animal models

Transcranial magnetic stimulation can modulate the excitability of the cortex

Cortical hyperexcitability may be a mechanism of migraine

*10 Hz stimulation of left dorsolateral prefrontal cortex

---

Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial


![Graph showing pain-free 2 hours after treatment](image)

- ITT: 22% (24% TMS vs 22% Sham)
- PP: 39% (43% TMS vs 24% Sham)

*P<0.018

---

Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial


![Graph showing sustained pain-free 24 and 48 hours after treatment](image)

- 24 hours: 16% (29% TMS vs 13% Sham)
- 48 hours: 13% (27% TMS vs 13% Sham)

*P<0.040

†P<0.003
UK Post Market Pilot Program

- 266 prescribed patients through 3/31/14
- Attacks treated including migraine with and without aura

- Acute response: reduction in pain severity, attack duration, acute medication use
- Preventive response: reduction in migraine days in both chronic and episodic migraine
- 67% renewal rate for those patients completing the 90-day evaluation period

<table>
<thead>
<tr>
<th>Variable # of pulses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single pulses: 10 patients</td>
</tr>
<tr>
<td>Double pulses: 66 patients</td>
</tr>
<tr>
<td>Triple pulses: 5 patients</td>
</tr>
<tr>
<td>&gt;Triple pulses: 24 patients</td>
</tr>
<tr>
<td>Daily use in some patients</td>
</tr>
</tbody>
</table>

Nerve Stimulation and Blocks

- New non-stimulators/neuro-nocodulators
  - Spring TMS® Total Migraine System
  - Cefaly

- Stimulators
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- Nerve Blocks—Practice Workshop
  - Occipital, supraorbital, supratrochlear, auriculotem poral

Sphenopalatine Ganglion
Sphenopalatine Ganglion

Sphenopalatine Ganglion Stimulation Using the ATI Neurostimulation System

Sphenopalatine Ganglion Stimulation Using the ATI Neurostimulation System

Patients hold the controller near the neurostimulator to apply therapy.


Sphenopalatine Ganglion Stimulation for Acute Treatment of Cluster Headache

- Patients (N=6) with refractory chronic cluster headache
- 18 attacks with visual analog scale (VAS) intensity of ≥8 (maximum = 10)
- Treated with short-term (up to 1 hour) electrical stimulation during maximal headache intensity

Results
- 61% (11/18) of attacks were completely resolved
- 17% (3/18) were partially resolved (>50% VAS reduction)
- 22% (4/18) had minimal relief in 4 attacks
- Associated autonomic features were resolved in each responder
- Pain relief was noted within several minutes of stimulation


Hypothalamic Deep Brain Stimulation
Hypothalamic Deep Brain Stimulation for Drug-resistant Chronic Cluster Headache

**Long-Term Data**
- Follow-up: median 8.7 years, range 6-12 years) in 17 patients
- Long-lasting improvement occurred in 70% of patients (12/17)

**Efficacy**
- 6 are persistently almost pain-free
- Stimulators off for a median of 3 years (range 3-4 years) in 5
- 6 no longer experience daily attacks
- Episodic CH interspersed with long-lasting remissions
- 1 did not improve
- 4 had bilateral CH, 3 developed tolerance after experiencing relief for 1-2 years

**Adverse Events**
- Electrode displacement (n=2)
- Electrode malpositioning (n=1)
- Persistent slight muscle weakness on one side (n=1)
- Infection (electrode n=3; generator n=1)
- Transient nonsymptomatic third ventricle hemorrhage (n=1)
- Seizure (n=1)


Rationale for Nerve Blocks in Headache

- New neurostimulators/neuromodulators
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    - Hypothalamic
- Nerve blocks—Practice Workshop
  - Occipital nerve, supraorbital, supratrochlear, auriculotemporal
**Rationale for Nerve Blocks in Headache**

- Patients intolerant of/partially responsive to medication
- Medical contraindications—pregnancy, planned pregnancy, nursing—specific treatments
- Presence of coexistent neck pain and tender trigger points
- Immediate relief from headache and associated symptoms
- Generally safe, relatively easy to perform
- Limited rigorous efficacy studies for headaches

**Occipital-Nuchal Pain in Primary Headache Disorders**

- Comparison of pain distribution in different headache disorders
- Cluster headache
- Chronic paroxysmal hemicrania

**Mechanisms of Pain Referral From Neck to Head**

- Trigeminal nucleus caudalis continuous with dorsal horn of upper 3 cervical spinal cord segments (trigemino-cervical complex)
Greater Occipital Nerve Block

- Pain referral from upper neck to head is bidirectional
- Decreasing afferent input to TNC
  - May relieve head pain because of decreased activation of central structures involved in pain perception
  - Anesthetic nerve block decreases afferent input
- Mechanism
  - May be unrelated to reducing local pain
  - Example: response to cluster headache V1 pain

Local Anesthetics

- Preferentially block sensory nerve fibers
  - Block pain fibers (Aδ, C)
  - Spare motor fibers (Aα)
- Basis of selective blockade—myelin sheath thickness affects drug penetration
- Bind to sodium channels, producing reversible conduction blockade—axons differ in sodium channel density

<table>
<thead>
<tr>
<th>Lidocaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical concentration</td>
<td>1-2% (10-20 mg/mL)</td>
</tr>
<tr>
<td>Duration of effect*</td>
<td>1-3 hours</td>
</tr>
<tr>
<td>Maximum dose*</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

*Subcutaneous injection
### Greater Occipital Nerve Block for Primary Headaches

#### Prolonged Effects from a Single Injection

<table>
<thead>
<tr>
<th>Headache Type (n)</th>
<th>Partial Response (%)</th>
<th>Complete Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine (54)</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Cluster (19)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>NDPH (10)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>HC (7)</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Other (11)</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean duration of complete response: 20 days
Mean duration partial response: 45 days
Mean latency to response: 2 days

---

### Adding Corticosteroid to Anesthetic

- **Mean headache severity before and 20 minutes after treatment**

- **Headache-free duration**
  - 2.7±3.8 days in A
  - 1.0±1.1 days in B (p=0.67)

- **Duration headache response**
  - 14.3±15.1 days in A
  - 5±4.9 days in B (p=0.60)

No significant differences between groups

---

### Greater Occipital Nerve Block for Cluster Headache

#### Study Design | n; Diagnosis | Intervention | Results
--- | --- | --- | ---
Retrospective⁴ | 14; ECH+CCH | A single GON block using lidocaine and triamcinolone | 64% of subjects became attack free for 3 to 70 days
Double blind, controlled⁵ | 23; ECH+CCH | A single GON block using lidocaine + betamethasone vs lidocaine + saline | 85% of subjects who received lidocaine + betamethasone became attack free within a week; 61% remained attack free for 4 weeks.
Case series⁶ | 15; CCH | A single GON block using prilocaine | 60% had minor headache improvement

ECH=episodic cluster headache; CCH=chronic cluster headache; n=number of subjects

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**Suboccipital Steroid Injections with Corticosteroid for Cluster Headache**

Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double blind, placebo controlled trial


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**Suboccipital Steroid Injections with Corticosteroid for Cluster Headache cont.**

Patients (%) with ≤2 attacks/day (mean) on Days 2–4 post-injection*

<table>
<thead>
<tr>
<th>Cortivasol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cluster</td>
<td>100</td>
</tr>
<tr>
<td>Episodic cluster</td>
<td>95</td>
</tr>
<tr>
<td>All</td>
<td>90</td>
</tr>
</tbody>
</table>

*L Primary efficacy endpoint


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**Adverse Events Reported with Corticosteroids for GON Block**

**Local**
- Alopecia
- Cutaneous atrophy (2 CDH patients received methylprednisolone 80 mg, 1-2x)

**Systemic**
- Cushing syndrome
- Woman with CDH received a total of 480 mg triamcinolone over 3 months

Greater Occipital Nerve Block for Short-term Migraine Prevention

**Double-Blind Randomized Controlled Trial**

- Adults (18–75 years old) with episodic or chronic migraine
- Primary endpoint: ≥50% reduction in frequency of moderate-severe headache days at 4 weeks
- Treatments
  - 2.5 ml 0.5% bupivacaine + 0.5 ml 20mg methylprednisolone over the ipsilateral or bilateral occipital nerve (n=34)
  - Placebo (n=35)
- 30% of patients in both groups met the primary endpoint (Δ0.00, 95% CI -0.22 to 0.23)
- Injection site pain (4 active, 2 placebo)


### Summary: Greater Occipital Nerve Block for Headache

- Experience suggests efficacy, though evidence is mixed, especially for migraine
- Best evidence for short-term cluster headache prophylaxis
- Occipital tenderness predicts favorable outcome
- Effect on headache pain may outlast its anesthetic effect
- Cluster studies have the best evidence for corticosteroids
- Safe and usually well-tolerated
- More controlled studies needed
- Unclear efficacy, safety, and role for repeated blocks at different intervals


### Injection Technique Considerations

- **Needle size**
  - 25-30 gauge needle
  - 1-10 ml syringe: depends on number of nerve injections and if targeting trigger points
- **Patient position:** depends on nerve being injected
  - Sitting
  - Lying down
- **Local anesthetic**
  - 1-2% lidocaine and/or bupivacaine 0.25-0.5%, 1:1 volume ratio
  - Add 40 mg triamcinolone or 20 mg methylprednisolone for cluster
**Nerve Blocks: Injection Volumes**

<table>
<thead>
<tr>
<th>Blocked nerve</th>
<th>Volume of injection (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater occipital</td>
<td>2-4</td>
</tr>
<tr>
<td>Lesser occipital</td>
<td>2-4</td>
</tr>
<tr>
<td>Auriculotemporal</td>
<td>1-2</td>
</tr>
<tr>
<td>Supraorbital</td>
<td>0.2-1</td>
</tr>
<tr>
<td>Supratrochlear</td>
<td>0.2-1</td>
</tr>
</tbody>
</table>


**Greater Occipital Nerve Block Technique**

- Identify nerve at scalp entry
  - Superior nuchal line
  - 1/3 distance between mastoid process and occipital protuberance
- 25 g needle inserted SC
- Infiltrate with:
  - 1-2% lidocaine and/or bupivacaine 0.25-0.5% (in a 1:1 volume ratio)
  - Add:
    - 20-40 mg methylprednisolone or
    - 4 mg dexamethasone

Ashkenazi et al. Wolff's Headache 8 ed.

**Auriculotemporal Nerve Block Technique**

- Use 30 gauge needle
- Inject 1-2 mL above posterior part of zygoma anterior to ear
- Feel for temporal artery pulse and avoid direct injection
- Additional injections may be made superiorly to block temporal area branches
Supratrochlear and Supraorbital Nerve Blocks Technique

Supratrochlear
- Use 30 gauge needle
- Inject 0.2–1 mL superomedial corner of orbit—at or just above eyebrow

Supraorbital
- Redirect needle 2 cm laterally
- Inject 0.2–1 mL
- Alternative: inject at or just above eyebrow, on midpupillary line

Myofascial Pain Syndrome

Trigger point: hyperirritable focus within muscle or its fascia

- Tender, taut band, twitch
- Refers pain to region corresponding to pain problem
- Existence/reliable identification may be difficult to establish
- Active trigger points
  - Found more often in patients with episodic TTH and migraine
  - Associated with greater attack frequency, duration, and severity

OnabotulinumtoxinA for Headache

What is OnabotA?

What are its indications?
What is OnabotA?

- A therapeutic neurotoxin derived from bacteria *Clostridium botulinum*; secretes 7 serotypes (A-G)
  - Blocks neurotransmitter release (exocytosis) at peripheral nerve terminals (sensory, cholinergic, adrenergic, serotonergic)
  - Cleavage target is SNAP-25 (t-snare), which attaches to syntaxin & the presynaptic membrane
- Approved treatment for cosmetic use and treatment of dystonia, spasticity, overactive bladder, hypersalaria, and chronic migraine

OnabotA and Pain Management

- OnabotA relieves pain in variety of conditions
  - Spasticity  - Trigeminal neuralgia
  - Back pain  - Neuropathic pain
- Peripheral injections of OnabotA inhibit sensitization of central V1 neurons in animal/human pain models
- Suggestion of central site of action
  - Bilateral effects from unilateral injection in experimental neuropathyt
  - Dissociation of analgesia and inflammation

OnabotulinumtoxinA for Headache

<table>
<thead>
<tr>
<th>What is OnabotA?</th>
<th>Therapeutic neurotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are its indications?</td>
<td></td>
</tr>
<tr>
<td>Does OnabotA work for headache?</td>
<td></td>
</tr>
</tbody>
</table>

**Does OnabotA Work for Headache?**

"PREEMPT" clinical trials program showed OnabotA to be effective in patients with CM

OnabotA not effective in episodic migraine

Currently, the only FDA-approved treatment for CM

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**OnabotulinumtoxinA: Pooled Efficacy at Week 24**

<table>
<thead>
<tr>
<th>Mean Change From Baseline</th>
<th>OnabotulinumtoxinA (n=680)</th>
<th>Placebo (n=696)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache days*</td>
<td>-8.4</td>
<td>-6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative headache hours on headache days</td>
<td>-119.7</td>
<td>-80.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Patients with severe (≥6) HT-6 score</td>
<td>67.6</td>
<td>78.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Frequency of migraine episodes</td>
<td>-4.9</td>
<td>-4.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Frequency of acute headache medication intake</td>
<td>-10.1</td>
<td>-9.4</td>
<td>0.247</td>
</tr>
</tbody>
</table>

*Primary Measure


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**OnabotulinumtoxinA Significantly Outperforms Placebo from 4–24 Weeks in CM**

Mean decrease in cumulative hours of headache on headache days

Weeks

![Graph showing the mean decrease in cumulative hours of headache on headache days over 24 weeks for OnabotulinumtoxinA and Placebo. The graph shows a significant difference with OnabotulinumtoxinA achieving a decrease of approximately 119.49 hours vs. Placebo at 24 weeks.]

OnabotulinumtoxinA Significantly Improves QoL in CM Patients from 4–24 Weeks (HIT-6)

*Change from Baseline in Mean Total HIT-6 Score

Change From Baseline in Weeks

Placebo (n=696)

*OnabotulinumtoxinA (n=688)

*Placebo (n=696)

*P<0.001

OnabotulinumtoxinA Significantly Improves QoL in CM Patients at Week 24 (MSQ)

Difference vs placebo exceeded the minimally important difference for MSQ on all parameters

P≤0.001 vs placebo

PREEPMT Studies: Responder Rates (≥50%) at Week 24

At Week 56, ≥70% of patients achieved ≥50% reduction in headache days¹ and migraine days² from baseline

OnabotA (n=688)  Placebo (n=696)

*P<0.001

¹Headache days at baseline: 19.9 OnabotA vs 19.8 placebo, P=0.498
²Migraine days at baseline: 19.1 OnabotA vs 18.9 placebo, P=0.328

PREEMPT: OnabotA Tolerability in CM

<table>
<thead>
<tr>
<th></th>
<th>OnabotA (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 parestis</td>
<td>15 (2.2)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

PREEMPT: Summary of Adverse Events
Pooled Data, Double-Blind Phase

| Participants (%)
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events (AEs)*</td>
</tr>
<tr>
<td>Treatment-related AEs†</td>
</tr>
<tr>
<td>Serious AEs</td>
</tr>
<tr>
<td>Treatment-related, serious AEs†</td>
</tr>
<tr>
<td>Discontinuations related to AEs‡</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
</tbody>
</table>

*All AEs include all reported events, regardless of relationship to treatment.
†Treatment-related AEs are those that in the investigator’s opinion may have been caused by the study medication with reasonable possibility (e.g. migraine requiring hospitalization).
‡The most frequently reported AEs leading to discontinuation in the OnabotA group were neck pain (8.0%), muscular weakness (5.5%), headache (3.4%), and migraine (3.4%).

PREEMPT Responder Rates (≥75%)
OnabotulinumtoxinA for Headache

<table>
<thead>
<tr>
<th>What is OnabotA?</th>
<th>Therapeutic neurotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are its indications?</td>
<td>For CM but not EM</td>
</tr>
<tr>
<td>Does OnabotA work for headache?</td>
<td></td>
</tr>
<tr>
<td>How do we think it works?</td>
<td></td>
</tr>
</tbody>
</table>

OnabotA Mechanism of Action

- **Muscle**
  - Reduction of muscle contractions (alpha motoneuron)
  - Reduction of la afferent via inhibition of muscle spindle (gamma motoneuron)
- **Antinociceptive**
  - Reduced muscle spasm–associated pain
  - Reduced nociceptive neuron activity
    - Neuropeptide release (peripheral pain sensation) inhibited; indirect CNS modulation
    - Direct CNS modulation

Sensitization of Peripheral Nociceptors
Sensitization of Trigeminovascular Neurons

OnabotA May Access Dural Afferent Nociceptors in Dermis/Subcutaneous Tissue

Reduction in primary sensory afferent signals from meninges, bone, and scalp

OnabotA May Access Dural Afferent Nociceptors in Dermis/Subcutaneous Tissue

Action potential
**Antinociceptive Effect in Trigeminal System**

Centrally Mediated and Dependent on Axonal Transport

Transport is Time-, Location-, and Dose-Dependent

May Explain Clinical Effect

**Pain Directionality and Prediction of OnabotA Response**

“My head feels like it’s going to explode”

“The left side of my head is splitting from the right”

“I’d like to drill a hole in my head to let the pressure out”
OnabotulinumtoxinA for Headache

- **What is OnabotA?**
  - Therapeutic neurotoxin

- **What are its indications?**
  - For CM but not EM

- **Does OnabotA work for headache?**
  - Yes

- **How do we think it works?**
  - Antinociceptive effects in the trigeminal system

- **How is OnabotA given for CM?**
PREEMPT Injection Paradigm

- **Landmarks** injected based on preceding phase 2 trials
- **Paradigm**: fixed-site, fixed-dose and modified follow-the-pain treatment model
  - 155 U of OnabotA at 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas
  - Up to additional 40 U OnabotA at another 8 sites using modified follow-the-pain strategy (maximum dose 195 U)
- Decision to inject additional OnabotA judgment of the pain treatment model trials injector

Injection Technique Considerations

- **Needle size**
  - 30-gauge with 1cc tuberculin syringe
- **Patient position**
  - Sitting for posterior injections
  - Lying for frontal and temporalis injections
- **Dilution**:
  - 50 unit (1ml normal saline)
  - 100 unit (2ml NS)
  - 200 unit (4ml NS)

Fixed-Site Fixed-Dose Injection Strategy

For each injection site, the injection volume is 0.1 mL (5 U)

- Corrugator 10U
- Procerus 5U
- Frontalis 20U
**Fixed-Site Fixed-Dose Injection Strategy**

- Temporals 20 U (each side)
- Occipitalis 30 U
- Cervical Paraspinal 20 U
- Trapezius 30 U

**Follow the Pain Strategy**

- Temporals 5 U/site (<2 additional sites)
- Occipitalis 5 U/site (<2 additional sites)
- Trapezius 5 U/site (<4 additional sites)