Comprehensive Migraine Education Program
Procedural Curriculum Developers

**PROGRAM CHAIRS**
David W. Dodick, MD, FAHS
Mayo Clinic College of Medicine

Richard B. Lipton, MD, FAHS
Albert Einstein College of Medicine

Stephen D. Silberstein, MD, FAHS
Thomas Jefferson College of Medicine

**COMMITTEE**
Andrew C. Charles, MD, FAHS
University of California, Los Angeles

Matthew S. Robbins, MD, FAHS
Montefiore Medical Center

Donna Gutterman, PharmD

Chris Caiazzo
Scottsdale injections workshop faculty

<table>
<thead>
<tr>
<th>Saturday, November 19, 2016</th>
<th>Sunday, November 20, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1:30 pm – 3:15 pm</strong></td>
<td><strong>8:00 am – 10:00 am</strong></td>
</tr>
<tr>
<td><strong>Concurrent Session V: Injections</strong></td>
<td><strong>Concurrent Session XI: Injections</strong></td>
</tr>
<tr>
<td>Moderator: Juline Bryson, MD, FAHS</td>
<td>Moderator: Juline Bryson, MD, FAHS</td>
</tr>
<tr>
<td><strong>1:30 pm – 1:35 pm</strong></td>
<td><strong>8:00 am – 8:05 am</strong></td>
</tr>
<tr>
<td>Introduction</td>
<td>Juline Bryson, MD, FAHS</td>
</tr>
<tr>
<td><strong>1:35 pm – 1:50 pm</strong></td>
<td><strong>8:05 am – 8:20 am</strong></td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Rashmi B. Halker, MD, FAHS</td>
</tr>
<tr>
<td>Matthew S. Robbins, MD, FAHS</td>
<td><strong>8:20 am – 8:35 am</strong></td>
</tr>
<tr>
<td><strong>1:50 pm – 2:05 pm</strong></td>
<td>Juline Bryson, MD, FAHS</td>
</tr>
<tr>
<td>Nerve Blocks</td>
<td><strong>8:35 am – 10:00 am</strong></td>
</tr>
<tr>
<td>Jessica Ailani, MD, FAHS</td>
<td>Juline Bryson, MD, FAHS</td>
</tr>
<tr>
<td><strong>2:05 pm – 3:15 pm</strong></td>
<td>Rashmi B. Halker, MD, FAHS</td>
</tr>
<tr>
<td>Hands-on Instruction</td>
<td>Amaal Starling, MD</td>
</tr>
<tr>
<td>Matthew S. Robbins, MD, FAHS</td>
<td>Bert B. Vargas, MD, FAHS</td>
</tr>
<tr>
<td>Jessica Ailani, MD, FAHS</td>
<td></td>
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<tr>
<td>Juline Bryson, MD, FAHS</td>
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<tr>
<td>Rashmi B. Halker, MD, FAHS</td>
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</tbody>
</table>
Dr. Ailani: speaker for Allergan and Teva. Speaker/consulting for Avanir. Advisory board/consulting for Eli Lilly. Stipend as section editor for *Curr Pain Headache Rep*.

Dr. Bryson: nothing to disclose.

Dr. Halker: nothing to disclose.

Dr. Robbins: site investigator for eNeura; institution receives support. Book royalties from Wiley. Stipend as section editor for *Curr Pain Headache Rep*.

Dr. Starling: consulting for Amgen. Advisory board and consulting for eNeura. Grant support from the Migraine Research Foundation.

Dr. Vargas: advisory boards with Alder, Avanir, and Pernix.
Learning Objectives

**IDENTIFY** headache patients who are candidates for:
- Nerve blocks
- OnabotulinumtoxinA

**EXPLAIN** the benefits and risks of extracranial nerve blocks and OnabotulinumtoxinA in headache and chronic migraine

**ACQUIRE** competency in performing:
- Occipital, supraorbital, supratrochlear, and auriculotemporal nerve blocks
- OnabotulinumtoxinA injections in patients with chronic migraine
What Are Nerve Blocks for Headache?
## Rationale for Nerve Blocks in Headache

<table>
<thead>
<tr>
<th>Medical contraindications for specific treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Planned pregnancy</td>
</tr>
<tr>
<td>• Nursing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coexistent neck pain and tender trigger points</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Immediate relief from headache and associated symptoms</td>
</tr>
<tr>
<td>• Generally safe, relatively easy to perform</td>
</tr>
<tr>
<td>• Limited rigorous efficacy studies for headaches</td>
</tr>
</tbody>
</table>
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

**Improves** non-headache symptoms: photophobia, allodynia, aura

**Mechanism**
- May be unrelated to reducing local pain
- Example: response to cluster headache V1 pain
Local Anesthetics

The Coca Plant

• 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
Local Anesthetics for Migraine

- Duration of nerve blockade depends on dose and pharmacokinetic properties of local anesthetic
- Longer than expected duration of analgesic (vs anesthetic) effect of nerve block is common
- Mechanism of prolonged analgesic effect incompletely understood

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical concentration</td>
<td>1-2% (10-20 mg/mL)</td>
<td>0.25%-0.5% (2.5-5 mg/mL)</td>
</tr>
<tr>
<td>Duration of effect*</td>
<td>1-3 hours</td>
<td>4-8 hours</td>
</tr>
<tr>
<td>Maximum dose*</td>
<td>300 mg</td>
<td>175 mg</td>
</tr>
</tbody>
</table>

*Subcutaneous injection
# Greater Occipital Nerve Block for Primary Headache

## Prolonged Effects from a Single Injection

<table>
<thead>
<tr>
<th>Headache Type</th>
<th>Injections Producing a Response (n)</th>
<th>&gt;30% Decrease in Severity or Frequency</th>
<th>Pain-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine (54)</td>
<td>17</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Cluster (19)</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>New daily persistent headache (10)</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hemicrania Continua (7)</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other (11)</td>
<td>5</td>
<td>2</td>
<td></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 in Migraine

Mean headache severity before and 20 minutes after treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache-free (days)</td>
<td>2.7±3.8</td>
<td>14.3±15.1</td>
<td>0.67</td>
</tr>
<tr>
<td>Headache response (days)</td>
<td>1.0±1.1</td>
<td>5±4.9</td>
<td>0.060</td>
</tr>
</tbody>
</table>


RCT in migraine (N=48)
- Lidocaine/triamcinolone vs lidocaine/saline
- NSD at 2, 4, and 8 weeks
## Greater Occipital Nerve Injection for Cluster Headache

<table>
<thead>
<tr>
<th>Design</th>
<th>Subjects (n)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Randomized, double blind, controlled¹      | ECH + CCH (23)        | Single GON block using lidocaine + **betamethasone** vs lidocaine + saline | • 85% attack-free within a week  
• 61% remained attack-free for 4 weeks |
| Randomized, double-blind, placebo-controlled² | CCH (15) ECH (28)    | 3 suboccipital injections of **cortivazol** 3.75 mg or placebo  
48-72 hours apart  
Add-on to verapamil | • ≤2 daily attacks: 95% cortivazol vs 55% controls (P=0.012)  
• Fewer attacks than controls in the first 15 days (mean 10.6 vs 30.3, P=0.004) |

ECH, episodic cluster headache; CCH, chronic cluster headache

Occipital steroid injection is the only cluster headache prophylactic therapy with 2 Class I studies and a Level A recommendation.
Adverse Events Reported with Corticosteroids for Greater Occipital Nerve Block

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

**Systemic**
- Cushing syndrome
- Woman with CDH received a total of 480 mg triamcinolone over 3 months\(^2\)

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# Double-Blind, Placebo-Controlled Studies of Peripheral Nerve Blocks or Injections for Migraine and Cluster Headache

<table>
<thead>
<tr>
<th>Study</th>
<th>Headache Disorder</th>
<th>N</th>
<th>Treatment</th>
<th>Primary Outcome Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilli et al</td>
<td>Episodic and chronic migraine</td>
<td>63</td>
<td>GON injection (U or B) with 2.5 ml 0.5% bupivacaine + 0.5 ml 20 mg methylprednisolone</td>
<td></td>
</tr>
</tbody>
</table>
GON injection (U or B) with 2.75 ml saline + 0.25 ml 1% lidocaine without epinephrine

≥50% reduction in frequency of moderate or severe HA days was 30% for both groups at 4 weeks (10/30 active vs 9/30 placebo, Δ0.00, 95% CI −0.22 to 0.23) |
| Inan et al  | Chronic migraine              | 72 | GON injection (U or B) with 1.5 ml of 0.5% bupivacaine + 1 ml of saline     | GON injection (U or B) with 2.5 ml saline                                                                                                                 | After 1 month:  
• HA days decreased from 16.9±5.7 to 13.2±6.7 with placebo ($P= .035$) and from 18.1±5.3 to 8.8±4.8 with active ($P< .001$) ($P= .004$ between groups)  
• HA hours decreased from 24.2±13.7 to 21.2±13.4 with placebo ($P=.223$) and from 25.9±16.3 to 19.3±11.5 with active ($P< .001$) ($P=.767$ between groups)  
• VAS score decreased from 8.1±0.9 to 6.7±1.6 with placebo ($P=.002$) and from 8.4±1.5 to 5.3±2.1 with active ($P< .001$) ($P=.004$ between groups) |
| Cuadrado et al | Chronic migraine           | 36 | GON (B) injection with 2 ml of 0.5% bupivacaine                               | GON (B) injection with 2 ml saline                                                                                                                     | After 1 week: Moderate-severe HA days reduced by -2 days (95% CI -2.7 to -1.3) with active vs -0.4 days (95% CI -1.4 to 0.5) with placebo ($P= .027$) |

U, unilateral; B, bilateral; GON, greater occipital nerve, HA, headache

Adapted from Robbins MS. Scientific American Neurology; 2016 (in press).
Peripheral Nerve Blocks in the Treatment of Migraine in Pregnancy

Shravya Govindappagari, MD, Tracy B. Grossman, MD, MSc, Ashlesha K. Dayal, MD, Brian M. Grosberg, MD, Sarah Vollbracht, MD, and Matthew S. Robbins, MD

Summary: Greater Occipital Nerve Block for Headache

- Occipital tenderness predicts favorable outcome
- Experience, preponderance of studies suggest efficacy and safety
- Effect on head pain may outlast its anesthetic effect
- Cluster studies have the best evidence for corticosteroids
- Safe and usually well-tolerated
- Unclear role for trigeminal and repeated blocks
- More controlled studies needed

**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
- For cluster, add:
  - 40 mg triamcinolone
  - 20-40 mg methylprednisolone
  - Dexamethasone 4 mg
# 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 subcutaneously

- **INFLTRATE** with:
  - 1-2% lidocaine and/or bupivacaine 0.25-0.5% (in a 1:1 volume ratio)
  - May add **one** of the following:
    - 20-40 mg methylprednisolone
    - 4 mg dexamethasone
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
## Potential Precautions and Contraindications

<table>
<thead>
<tr>
<th>Patients</th>
<th>Concern</th>
<th>Action</th>
</tr>
</thead>
</table>
| Local anesthesia allergy | Allergic reaction, including anaphylaxis | • PNB with local anesthetic contraindicated  
• Use corticosteroids only |
| Elderly              | Hypotension                       | • Reduce anesthetic concentration; avoid lidocaine 5%  
• Limit number of nerves to be blocked  
• Restrict PNB to unilateral GON injection |
| Pregnant             | Teratogenicity                    | • Use lidocaine over bupivacaine  
• Avoid betamethasone and dexamethasone  
• Use any corticosteroids with caution |
| Vasovagal attacks*   | Vasovagal reaction               | • Perform PNB in supine position, where feasible |
| Syncopal attacks*    | Presyncope or syncope             | • Use bupivacaine instead of lidocaine  
• Reduce concentration of anesthetic agent  
• Allow for extra time in the supine position after the procedure as a precaution |

*Prior

### Potential Precautions and Contraindications (cont.)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Concern</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open skull defect Craniotomy</td>
<td>Intracranial diffusion of anesthetic agent</td>
<td>PNB contraindicated</td>
</tr>
<tr>
<td>Anticoagulation therapy Antiplatelet therapy</td>
<td>Hematoma</td>
<td>Extra attention to palpate for (and avoid) neighboring arteries (occipital, temporal) Compress at each PNB site for 5-10 minutes</td>
</tr>
<tr>
<td>Cosmetic concerns</td>
<td>Alopecia</td>
<td>Avoid corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Cutaneous atrophy</td>
<td>If methylprednisolone must be used, dose &lt;80 mg in GON region</td>
</tr>
</tbody>
</table>

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

Found in some pain-free controls

Injection Technique

- **Seated or recumbent** position
- **22-30 gauge**, 1.5-inch needle
- **Hold overlying skin** and stabilize between thumb and index finger
- **Insert** 1–1.5 cm away from the trigger point
- **Advance** at 30°
- **Local** anesthetics
  - 0.1–0.3 cc of 1% lidocaine or 0.5% bupivacaine
  - 1-4 mL per site

Injection Technique \textit{cont.}

3 most common muscles

\begin{itemize}
\item \textbf{TRAPEZIUS}
\item \textbf{STERNOCLIDOMASTOID}
\item \textbf{TEMPORALIS}
\end{itemize}

Sphenopalatine Ganglion

- Key peripheral structure responsible for expression of cranial autonomic symptoms
- Though a parasympathetic ganglion, it has sympathetic and trigeminal inputs, as well as a direct connection to V2
- Sphenopalatine ganglion stimulation
  - Increases cerebral blood flow
  - Leads to release of Ach, VIP, NO in dural vessels, leading to plasma protein extravasation, neurogenic inflammation, and activation of trigeminal nociception

Intranasal Lidocaine for Treatment of Migraine
A Randomized, Double-blind, Controlled Trial
Morris Maizels, MD; Barbara Scott, MD; Wendy Cohen, MD; Wansu Chen, MS

Results with SPG Blockade

**CHRONIC MIGRAINE** (N=38)\(^1\)
- B/L SPG blocks twice per week for 6 weeks
- Significant reductions vs placebo at 15 minutes, 30 minutes, and 24 hours post-treatment ($P<0.001$ for all time points)
- HIT-6 scores significantly decreased from before treatment to the final treatment ($P=0.005$) vs NSD in the placebo group
- No significant or lasting adverse events
- Secondary endpoints\(^2\): Decreased headache days at 1 month, HIT-6 scores at 1 and 6 months, and medication usage; trends but NSD vs placebo

**EMERGENCY DEPARTMENT**: acute anterior or global-based headache\(^3\)
- 50% pain reduction: 48.8% bupivacaine vs 41.3% placebo (NSD)
- 24-hour headache-free: 24.7% difference (95% CI 2.6%–43.6%)
- 24-hour nausea free: 16.9% difference (95% CI 0.8% to 32.5%)

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What Is OnabotulinumtoxinA (onabotA)?
**THERAPEUTIC NEUROTOXIN** derived from bacteria *Clostridium botulinum*

**SECRETES** 7 serotypes (A-G)

**BLOCKS** neurotransmitter release at peripheral nerve terminals
- Sensory
- Cholinergic
- Adrenergic
- Serotonergic

**Cleavage Target:** SNAP-25 (t-snare)—attaches to syntaxin & the presynaptic membrane

http://neuromuscular.wustl.edu/nother/bot.htm

*Image courtesy of CDC*
What Are Its Indications?

**APPROVED TREATMENT** for cosmetic use and treatment of:

- Dystonia
- Spasticity
- Overactive bladder
- Hypersialorrhea
- Chronic migraine

http://neuromuscular.wustl.edu/nother/bot.htm
OnabotulinumtoxinA and Pain Management

• **Relieves pain** in variety of conditions
  - Spasticity
  - Trigeminal neuralgia
  - Back pain
  - Neuropathic pain

• **Peripheral injections** inhibit sensitization of central V1 neurons in animal/human pain models\(^1-^5\)

• **Central site** of action (suggested)\(^6\)
  - Bilateral effects from unilateral injection in experimental neuropathy
  - Dissociation of analgesia and inflammation

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Does OnabotulinumtoxinA Work for Headache?

Not effective in patients with episodic migraine

The only FDA-approved treatment for chronic migraine

“PREEMPT“ clinical trials: OnabotulinumtoxinA was effective in chronic migraine
## OnabotulinumtoxinA: Pooled Efficacy at Week 24

<table>
<thead>
<tr>
<th>Mean Change From Baseline</th>
<th>OnabotulinumtoxinA (n=688)</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 (≥60) HIT-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>

OnabotulinumtoxinA Significantly Outperforms Placebo from 4–24 Weeks in Chronic Migraine

Mean decrease in cumulative hours of headache on headache days

Weeks

Hours of Headache Days

OnabotulinumtoxinA (n=688)

Placebo (n=696)

−80.49

−119.67

* P<0.001

At Week 56, ≈70% of patients achieved ≥50% reduction in headache days\(^1\) and migraine days\(^2\) (from baseline)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Headache Days(^1)</th>
<th>Migraine Days(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA (n=688)</td>
<td>47.1</td>
<td>35.1</td>
</tr>
<tr>
<td>Placebo (n=696)</td>
<td>48.2</td>
<td>36.4</td>
</tr>
</tbody>
</table>

1. Headache days at baseline: 19.9 OnabotulinumtoxinA vs 19.8 placebo, \(P=0.498\)
2. Migraine days at baseline: 19.1 OnabotulinumtoxinA vs 18.9 placebo, \(P=0.328\)

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

<table>
<thead>
<tr>
<th>Participants (%)</th>
<th>OnabotA (n=687)</th>
<th>Placebo (n=692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs*</td>
<td>62.4</td>
<td>51.7</td>
</tr>
<tr>
<td>Treatment-related AEs†</td>
<td>29.4</td>
<td>12.7</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>4.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Treatment-related serious AEs†</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Discontinuations related to AEs§</td>
<td>3.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Includes all reported events, regardless of relationship to treatment.

†AEs that in the investigator’s opinion may have been caused by the study medication with reasonable possibility (n=1 migraine attack requiring hospitalization).

§The most frequently reported AEs leading to discontinuation in the OnabotulinumtoxinA group were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%).

### PREEMPT: OnabotulinumtoxinA Tolerability in Patients with Chronic Migraine

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>OnabotulinumtoxinA (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>

How do we think it works?
OnabotulinumtoxinA 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
OnabotulinumtoxinA May Access Dural Afferent Nociceptors in Dermis/Subcutaneous Tissue

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

OnabotulinumtoxinA May Access Dural Afferent Nociceptors in Dermis/Subcutaneous Tissue

Antinociceptive Effect in Trigeminal System

Centrally Mediated and Dependent on Axonal Transport

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

May Explain Clinical Effect

Saline control  BTX-A 1 day  BTX-A 3 days  BTX-A 5 days
Saline control  BTX-A 3.5 U/kg  BTX-A 15 U/kg  BTX-A 30 U/kg

Pain Directionality and Prediction of Response to OnabotulinumtoxinA

Upregulation Of Inflammatory Gene Transcripts in Periosteum of Chronic Migraineurs

• Measured the expression of gene transcripts (mRNA) encoding proteins in patients with:
  – Attacks associated with muscle tenderness
  – No history of headache

• In patients with muscle tenderness:
  – Proinflammatory genes (eg, CCL8, TLR2) significantly increased
  – Anti-inflammatory genes (eg, IL10RA, CSF1R) decreased

• Inflamed molecular environment surrounding periosteal pain fibers activates trigeminovascular nociceptors through:
  – Suture branches of intracranial meningeal nociceptors
  – Somatic branches of the occipital nerve

Implications for the Extracranial Origin Of Headache


Implications for Predicting OnabotulinumtoxinA Responders
# OnabotulinumtoxinA for Headache: Review

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is OnabotulinumtoxinA?</td>
<td>Therapeutic neurotoxin</td>
</tr>
<tr>
<td>What are its indications?</td>
<td>Dystonia, spasticity, overactive bladder, hypersialorrhea, chronic migraine</td>
</tr>
<tr>
<td>Does OnabotulinumtoxinA work for headache?</td>
<td>For chronic migraine, not episodic migraine</td>
</tr>
<tr>
<td>How do we think it works?</td>
<td>Antinociceptive effects in the trigeminal system</td>
</tr>
</tbody>
</table>

**How is OnabotulinumtoxinA given for chronic migraine?**
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 OnabotulinumtoxinA at 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas
  - Up to additional 40 U OnabotulinumtoxinA at another 8 sites using modified follow-the-pain strategy (maximum dose 195 U)

• **Decision to Inject** additional OnabotulinumtoxinA judgment of injector

Injection Technique Considerations

**Needle Size**
- 30-gauge with 1 cc tuberculin syringe

**Patient Position**
- Sitting for posterior injections
- Lying for frontal and temporalis injections

**Dilution**
- 50 unit (1 ml normal saline)
- 100 unit (2 ml NS)
- 200 unit (4 ml 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

- **Temporalis**: 20 U*
- **Occipitalis**: 30 U
- **Cervical Paraspinal**: 20 U
- **Trapezius**: 30 U

*Each side
Follow the Pain Strategy

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