# *Botulinum Neurotoxins in Headache Management; Vienna 2013*


## *Stephen D Silberstein, MD*

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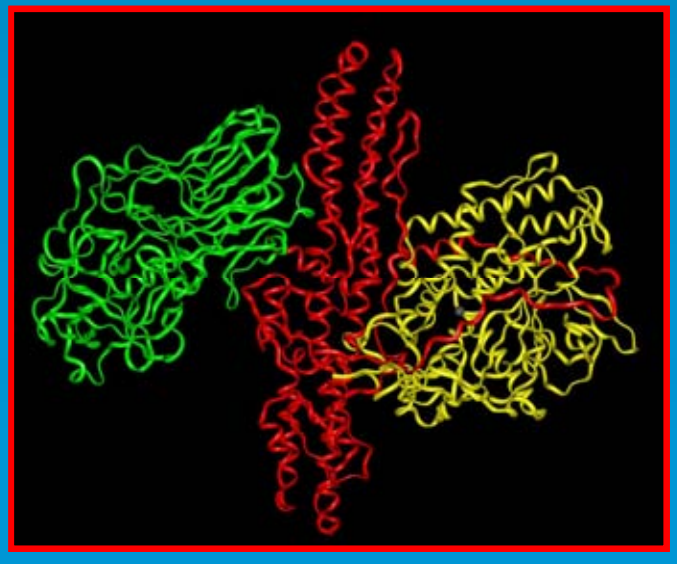
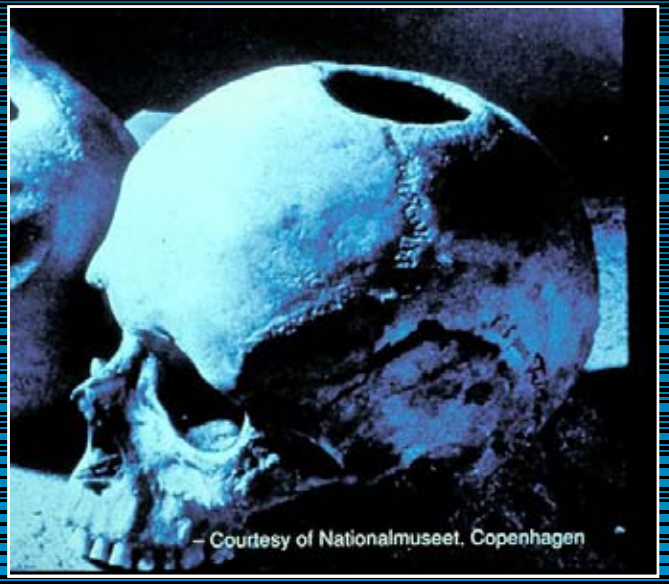
*Philadelphia, Pa. USA*

# *Headache: A Common Costly Health Problem*

- *Headache* has troubled humankind from dawn of civilization
- Evidence of trepanation, early form of neurosurgery, found on skulls from 7000 BC
- Migraine symptoms, including headache, aura, prodrome, nausea, vomiting, and familial tendency, described for over 1,000 years



# *Migraine*

- Primary headache disorder
- Headaches typically unilateral, throbbing
  - Associated with  nausea, vomiting, sensitivity to light, sound, and head movement
  - Auras, usually visual, occur ~15-20% of patients
- Migraine can be episodic (<15 days per month) or chronic (?15 days per month > 3 months)

# *ICHD-3?|Chronic Migraine (CM)*

A. Headache ≥ 15 days/month for ≥3months

B. Patient *had* ≥ 5 attacks fulfilling ICHD-2 *Migraine without aura*

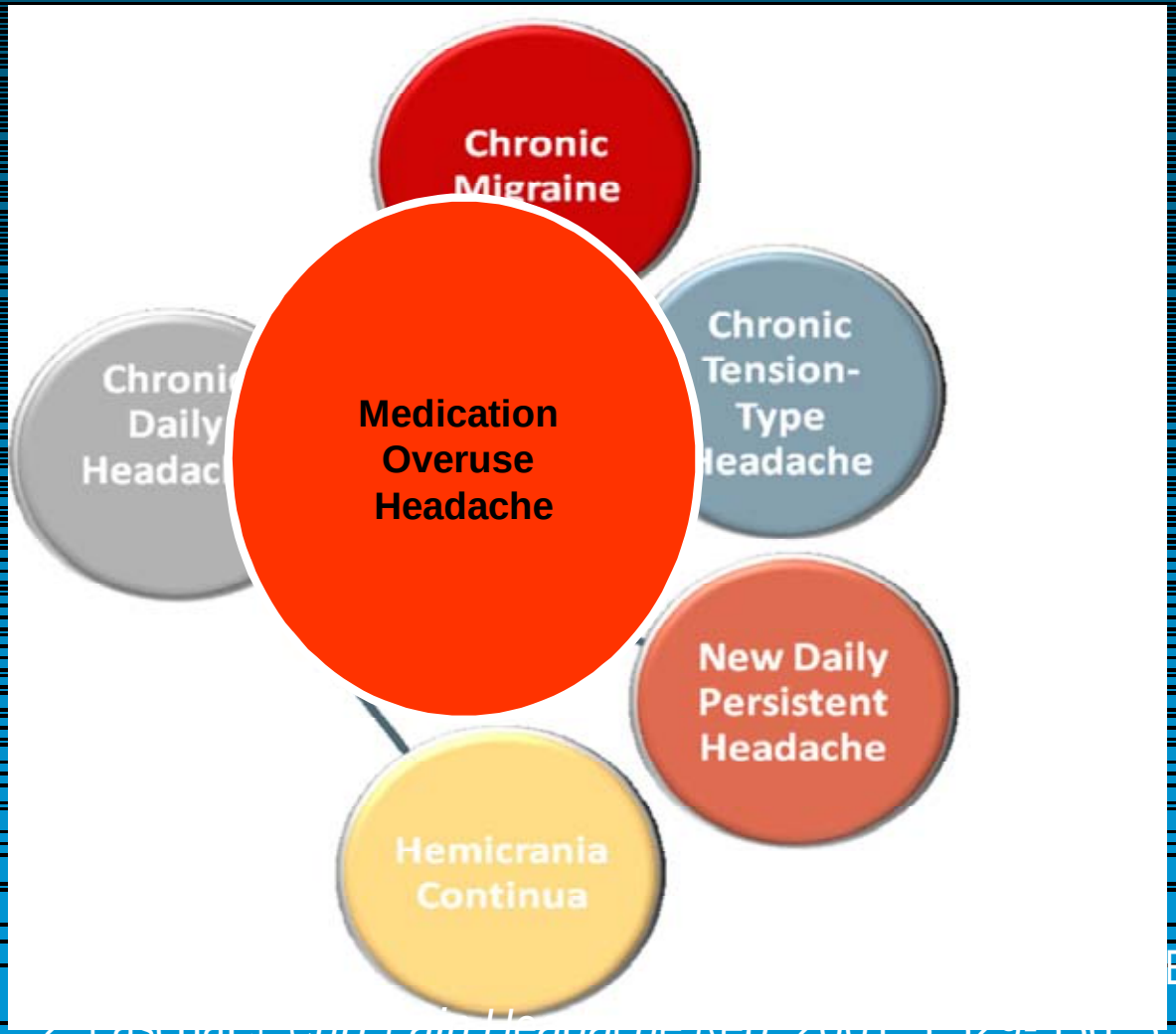
C. On ≥ *8*days/month for ≥3months headache fulfils criteria for ***migraine w or w/o aura*** and/or treated and relieved by triptan(s) or ergot

D. *Not better accounted for by another ICHD-3 diagnosis*

**CM and medication overuse should have both diagnoses**

# *Chronic Migraine is a CDH Subtypes*

Chronic Daily Headache Subtypes




Frequency: ?Ï15 headache days/month

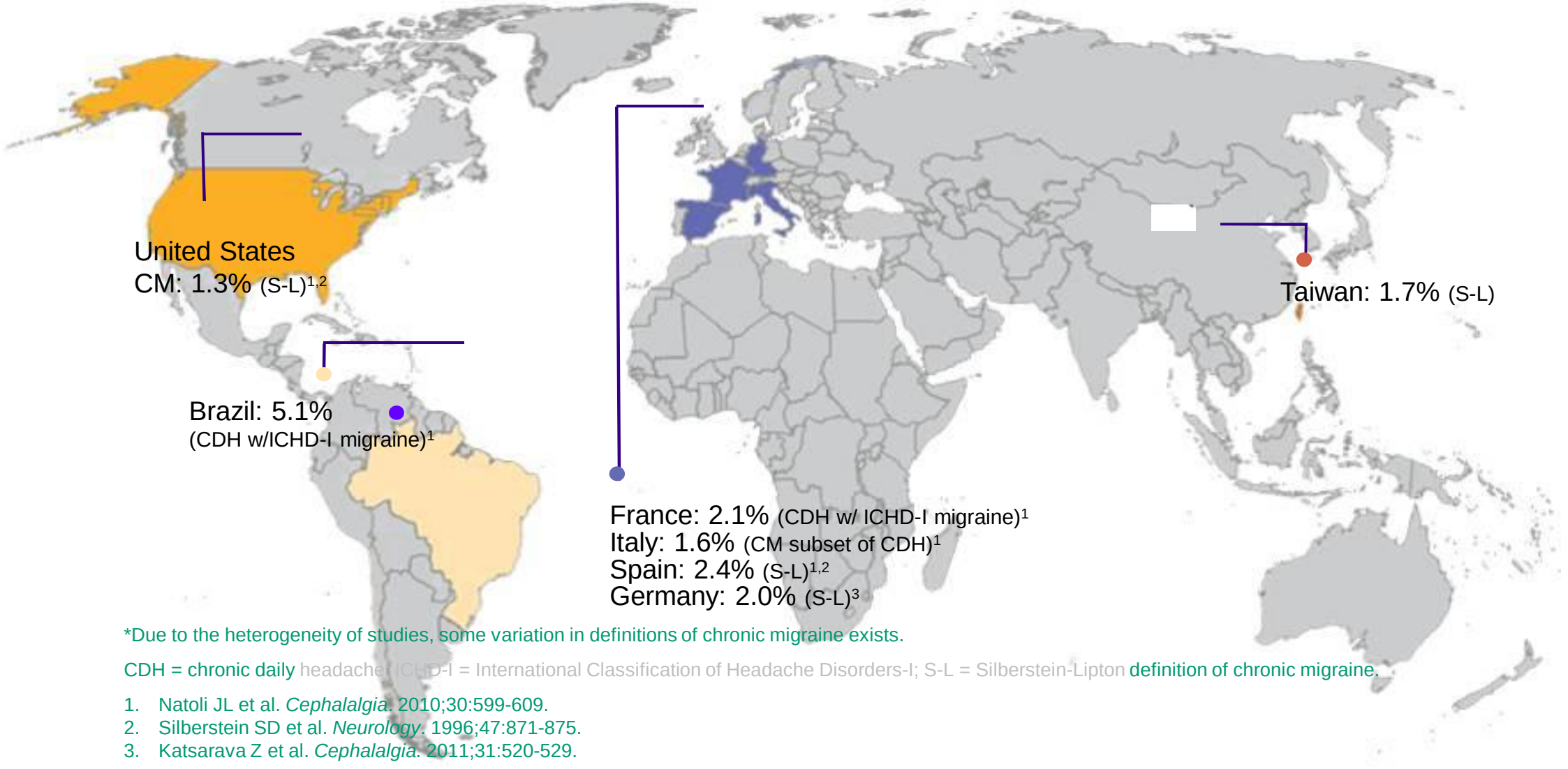
Duration: Headache lasting >4 hours

**Subclassified *with* and *without* medication overuse**

Most common form of chronic daily headache is **chronic migraine**

E et al. *J Headache Pain*. 2007; 8:263-272.
2. Pascual J. *Curr Pain Headache Rep*. 2001;5:329-336. 3. Sanin LC. *Cephalalgia*. 1994;14:443- 446.

# *Chronic Migraine: Global Prevalence*




*Due to the heterogeneity of studies, some variation in definitions of chronic migraine exists.

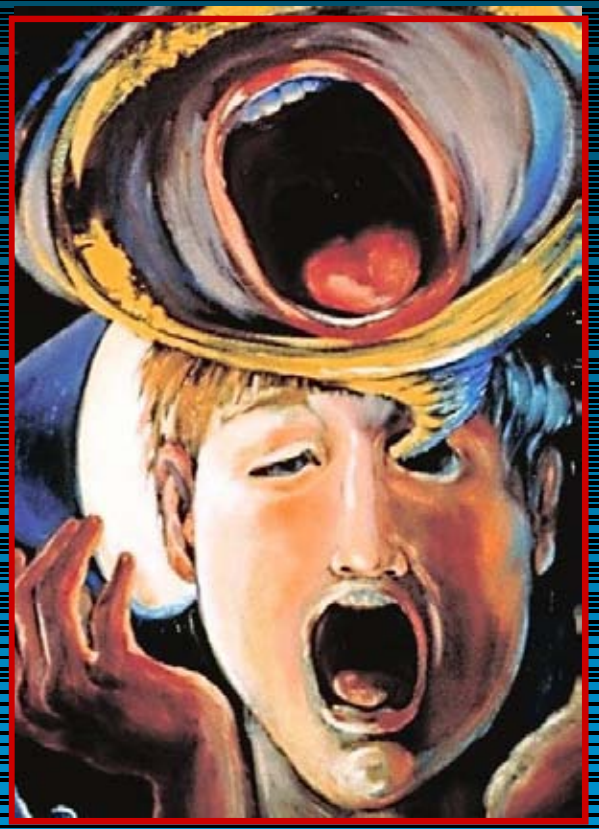
CDH = chronic daily headache; ICHD-I = International Classification of Headache Disorders-I; S-L = Silberstein-Lipton definition of chronic migraine.


1. Natoli JL et al. *Cephalalgia*. 2010;30:599-609.
2. Silberstein SD et al. *Neurology*. 1996;47:871-875.
3. Katsarava Z et al. *Cephalalgia*. 2011;31:520-529.

# *Headache Treatment*

**Depends on:**

- Making an accurate diagnosis
- Ruling out alternative etiologies
- Ordering appropriate studies
- Addressing headache's impact



**Ultimate Goal: Headache Relief**

Patients want to know what is wrong and that their complaints are taken seriously

# *Acute vs Preventive Therapy*

Acute (Abortive)

- Taken after attack has begun to relieve pain and disability and stop progression

Preventive

- Taken to reduce attack frequency, severity, and duration
- Patients can also use acute treatment


OCTOBER 7, 2002
TIME
Preventing
HEADACHES
The latest research offers new hope for all of us
www.time.com AOL Keyword: TIME

# *Consider Migraine Prevention*

1. **Attacks significantly interferes with patients‘ daily routine, despite appropriate acute treatment**
2. **Frequency attacks (>4 attacks/month); risk of CDH**
3. **Acute Rx overuse (≥2 days/week); risk of MOH**
4. **Contraindication, failure, or intolerance to acute Rx**
5. **Presence of certain disorders**

   Prolonged, disabling, or frequent aura

   Hemiplegic Migraine  Basilar Migraine  Migrainous Infarction
6. **Patient preference**

# *Preventive Medications*

- **Anticonvulsants**
  - **Divalproex***
  - Gabapentin
  - **Topiramate***
- **Antidepressants**
  - TCAs, SSRIs, SNRIs
- **B-Blockers**
  - **Propranolol*/ Timolol***
- **Ca channel blockers**
  - Verapamil
- **NSAIDs**
- **5-HT antagonists**
  - **Methysergide***/methergine
- **Neurotoxins**
  - OnabotulinumtoxinA (CM)*
- **Angiotensin system**
  - Ace inhibitors
  - Antagonists
- **Acetyl-Cholinesterase inhibitors?**
- **Other**
  - Riboflavin, Coenzyme Q10, Feverew, Petasites
  - Neuroleptics?

***FDA Approved**

# *Migraine: Neurovascular Pain Syndrome*

**Initiation: Central facilitation**

- Prodrome: Hypothalamic activation
- Aura: CSD triggered in hypersensitive cortex
- Headache: Referred pain from dura mater and blood vessels
  - Aura activates meningeal nociceptors
  - Direct nociceptor activation via parasympathetics?
- Meningeal nociceptor activation associated with
  - Neurogenic inflammation (NI)
  - Peripheral sensitization

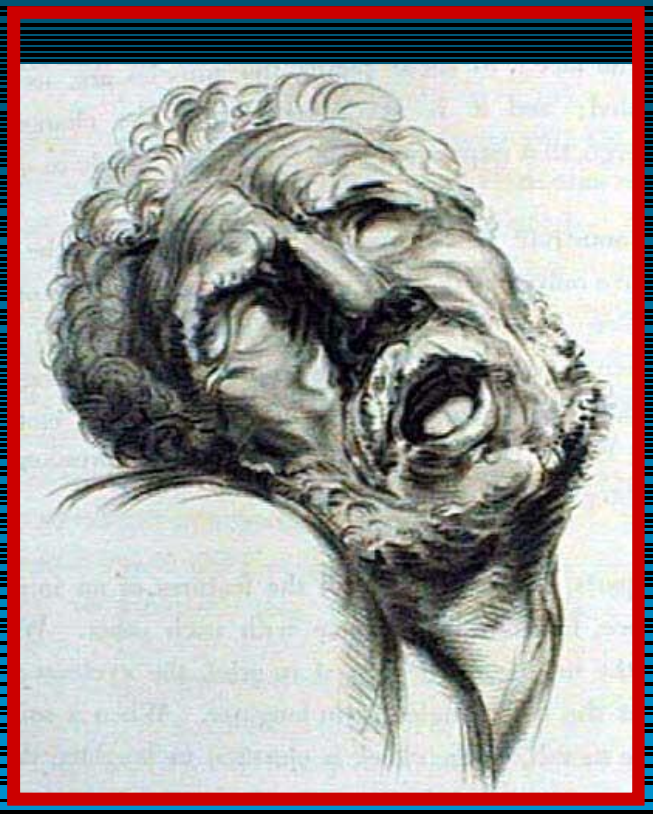
**Persistence: Central sensitization**

# *Migraine Prevention Mechanisms*

- Raise threshold to migraine activation
  - Inhibit migraine generator
  - Enhance antinociception
  - Inhibit cortical spreading depression
  - Inhibit sensitization
  - Block neurogenic inflammation
- Stabilize more reactive nervous system
  - Modulate sympathetic or serotonergic tone

# *BTX-A: Pain and Headache*

- Pain improved in initial dystonia and spasticity studies
- Brin 1986: cervical dystonia
  - 64% *motor* improvement
  - 74% *pain* improvement



Facial expression of pain drawn by Sir Charles Bell (*The Anatomy and Philosophy of Expression* London : Henry G. Bohn, 1865)

# *Pharmacology of Botulinum Toxin*

- 7 distinct antigenic types (serotypes):
  - $A_{1-4}$, B, C, D, E, F, G
    - Available preparations of A toxin belong to subtype A1
    - A2 more potent neuromuscular blocker than A1 toxins
- All inhibit acetylcholine release
- Serotypes differ
  - Biochemical structure and molecular weight
  - Potency ($ED_{50}$)
  - Intracellular target

# *Botulinum Toxins*

Botulinum toxin type A (subtype A1)

- OnabotulinumtoxinA (BOTOX® Allergan)
- AbobotulinumtoxinA (Dysport® Ipsen)
- IncobotulinumtoxinA (XEOMIN® Merz)

Botulinum toxin type B

- RimabotulinumtoxinB (Myobloc®/Neurobloc® Solstice)

Botulinum toxin type F being developed for clinical use

# *BTX Mechanism of Action*

- Muscle
  - Reduction of muscle contractions (alpha motoneuron)
  - Reduction of Ia afferent via inhibition of muscle spindle (gamma motoneuron)
- Antinociceptive
  - Reduced nociceptive neuronal activity
    - Neuropeptide release inhibited
    - Inhibits peripheral sensitization
      - Results in indirect reduction of central sensitization

# *Migraine and Sensitization*

**Peripheral sensitization of trigeminovascular neurons**

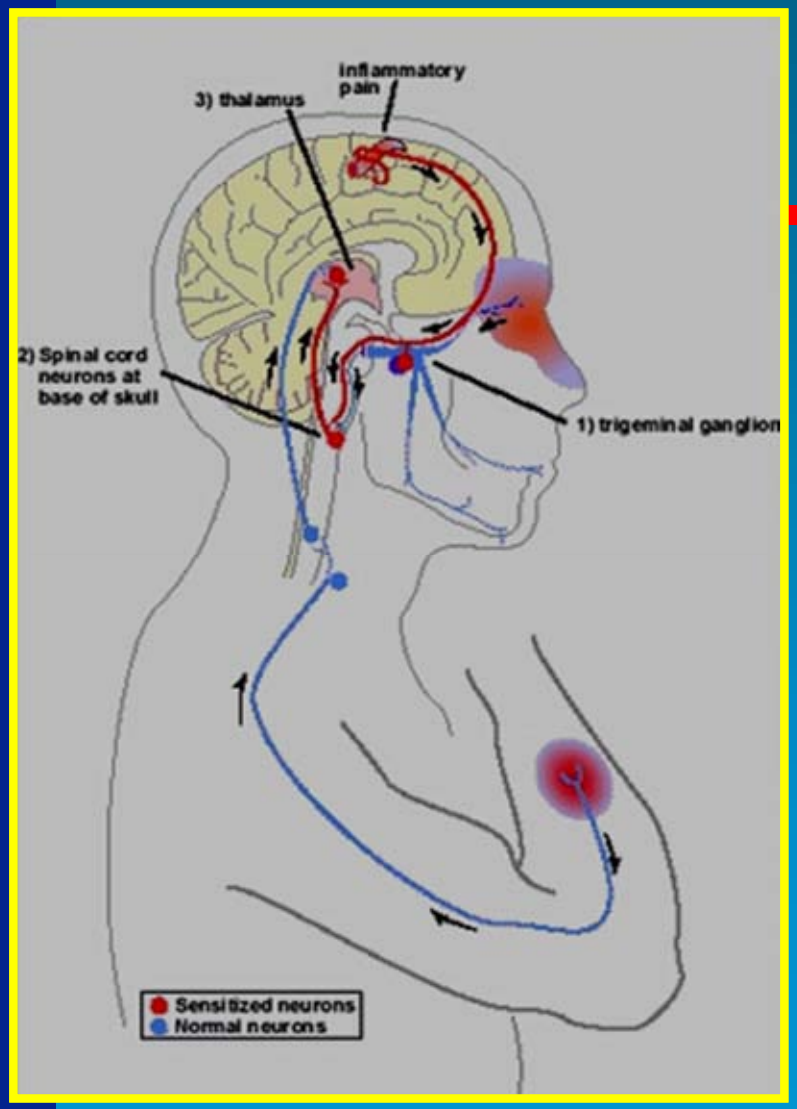
Mediates throbbing pain and its worsening by bending over

Central sensitization of trigeminovascular neurons in nucleus caudalis

Mediates scalp tenderness and increased periorbital skin sensitivity (i.e., cutaneous allodynia)

Allodynia: non painful stimuli are painful

# *Cutaneous Allodynia and Migraine*




*Burstein et al. Ann Neurol 2000;*
*Burstein et al. Headache 2002.*

Migraineurs develop increased sensitivity to stimuli due to increased nerve excitability

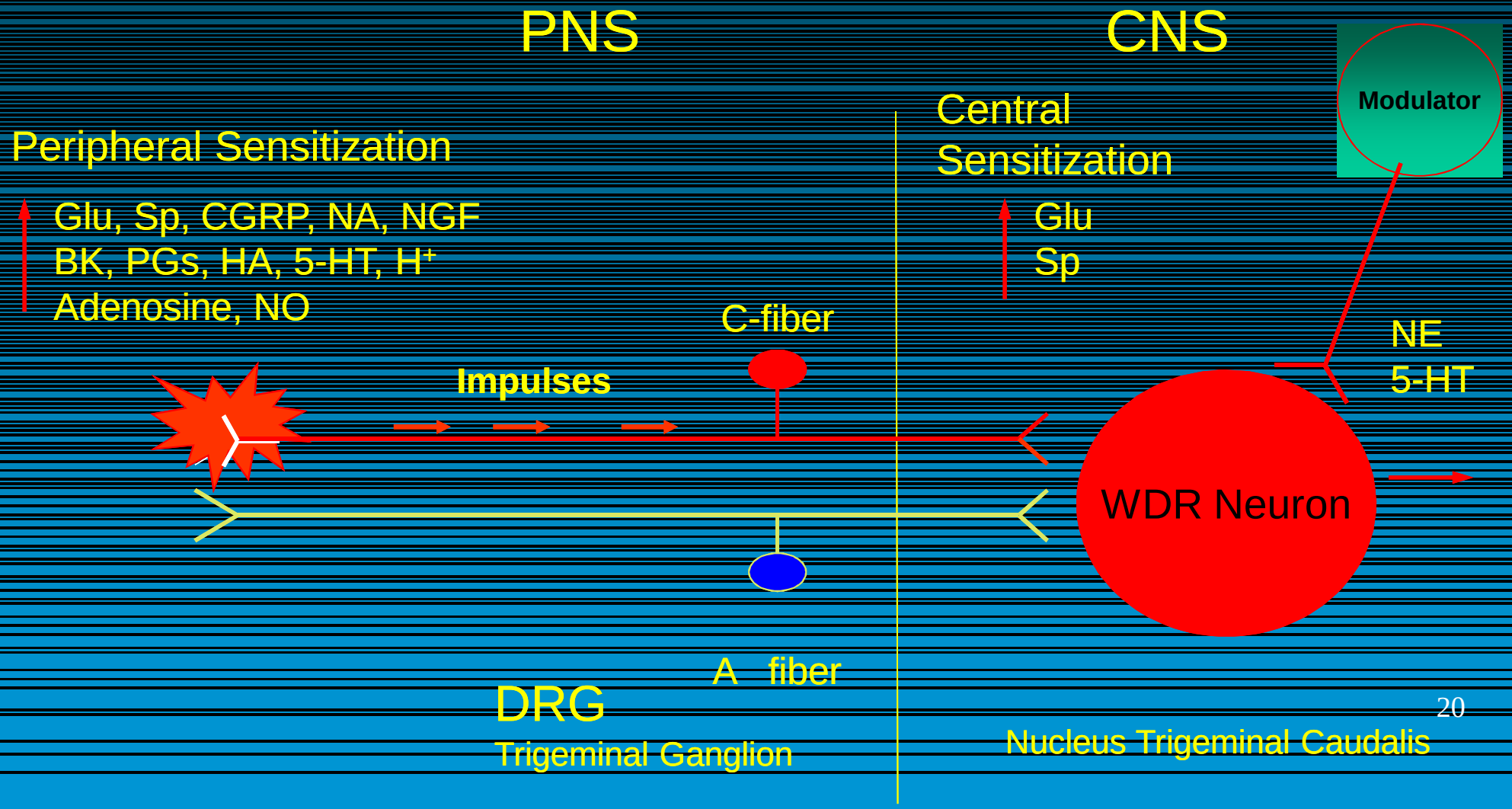
80% of migraine patients suffered from *cutaneous allodynia* during attacks

Due to central sensitization

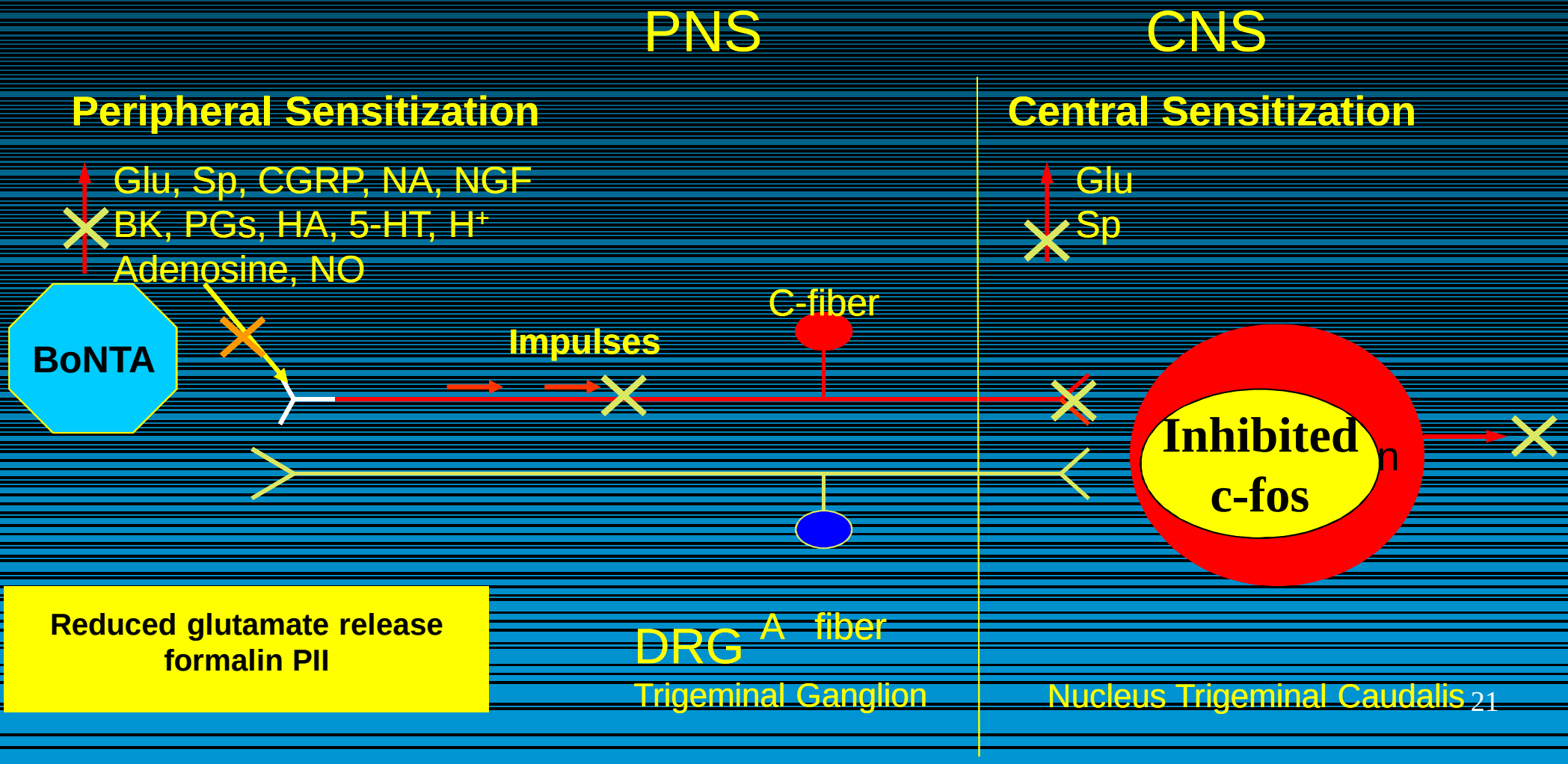
After allodynia occurs, triptans lose effectiveness

***TREAT EARLY!***

# *Sensitization and Migraine*



# *BTX-A Mechanism of Action: Inhibits NT Release*

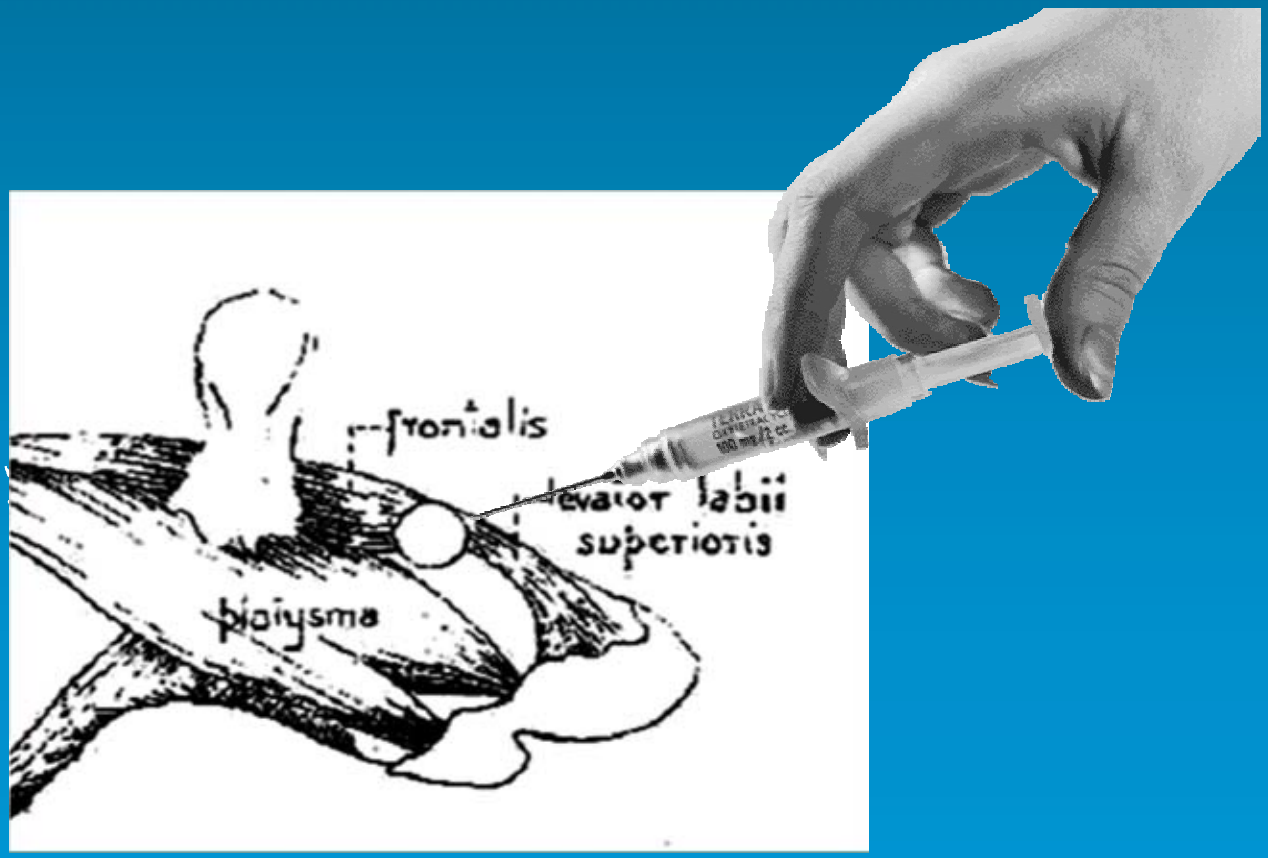


# *Botulinum Toxin Type A Inhibits Induction of Sensitization of 2nd Sensory Neurons in the Trigeminal Nucleus Caudalis*

Michael L. Oshinsky, PhD,
Jia Luo, MD, Patricia Pozo-Rosich, MD, Shay Hyman,
Stephen Silberstein, MD

Thomas Jefferson University
Philadelphia, PA

# *Injection Site*




3 or 7.5 units Botx-A in 10 µl saline

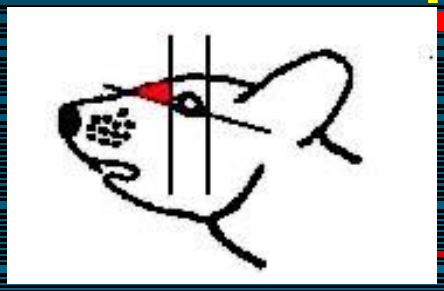
**Subcutaneous Muscles in Rat**
**(adapted from Anatomy of the Rat, Green 1963)**

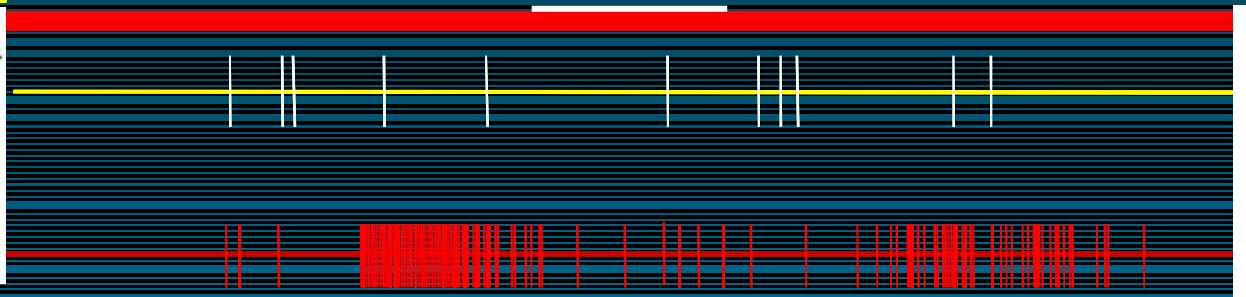
# *Central Sensitization*

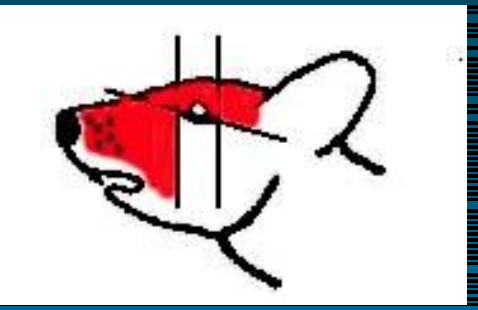
**Before soup**

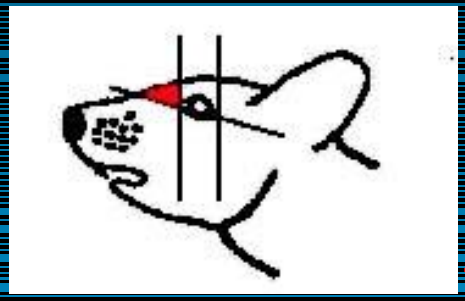
**BRUSH**

**2.5 hrs after soup**









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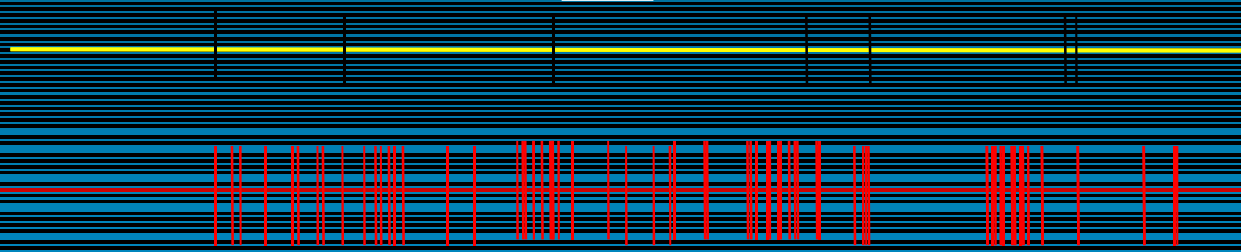
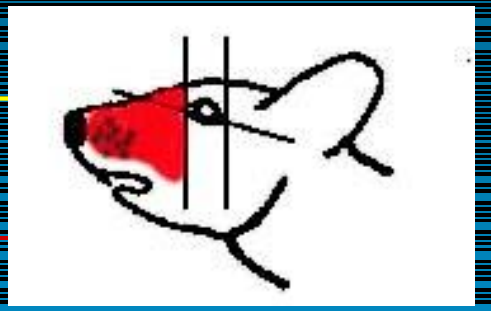
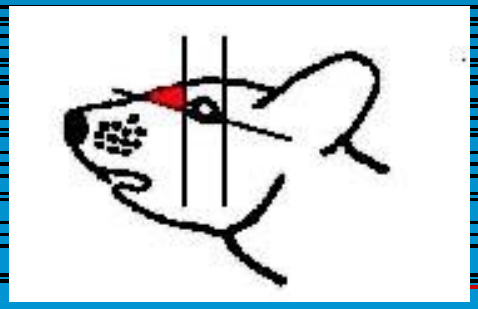
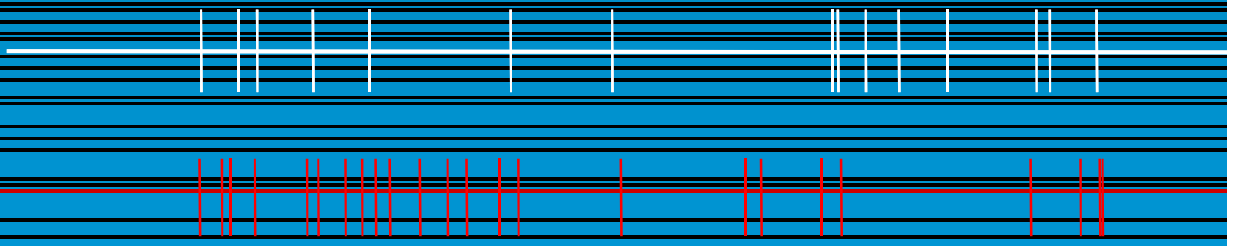
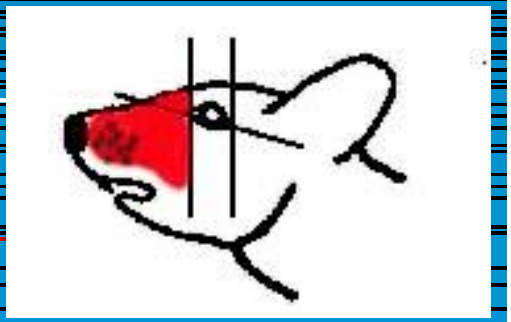






**PRESSURE**





stimulus

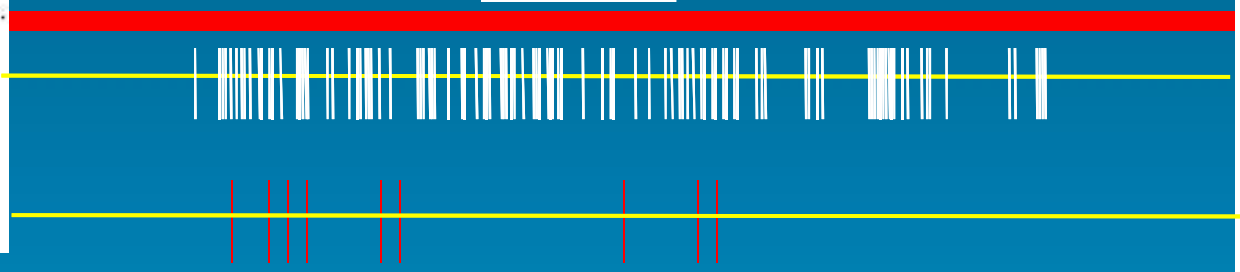
1 sec

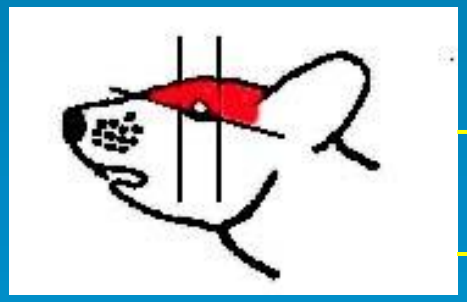
# *Pretreatment with BTX-A* (7.5U)

Before soup

BRUSH

2.5 hrs after soup





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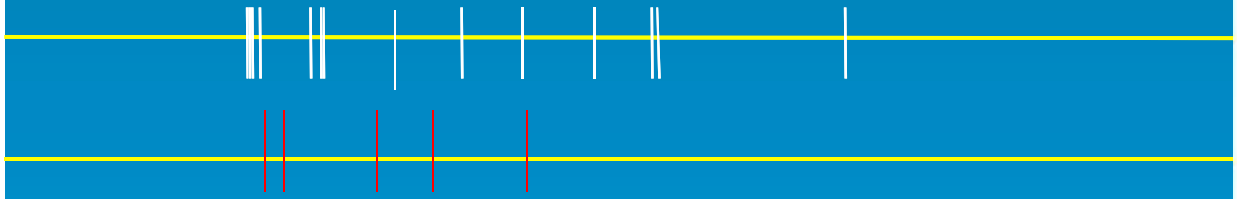

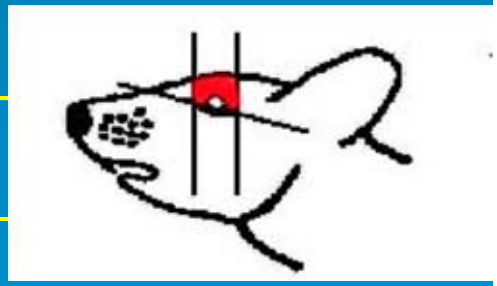

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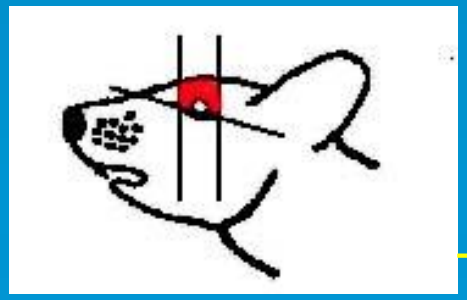
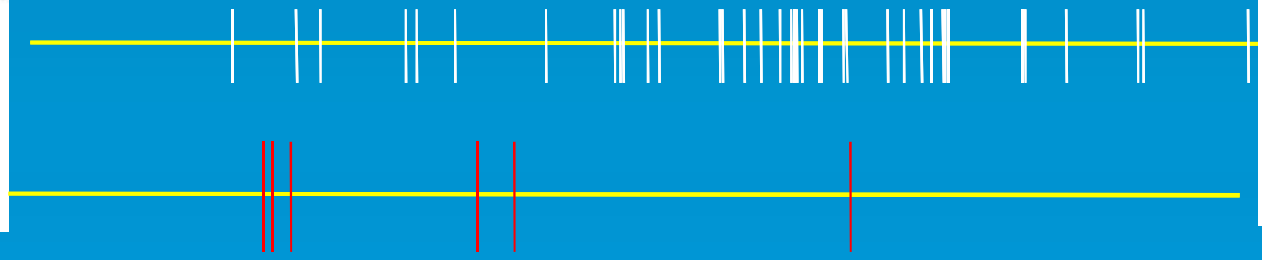
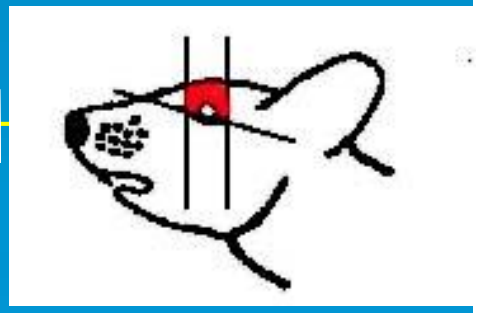


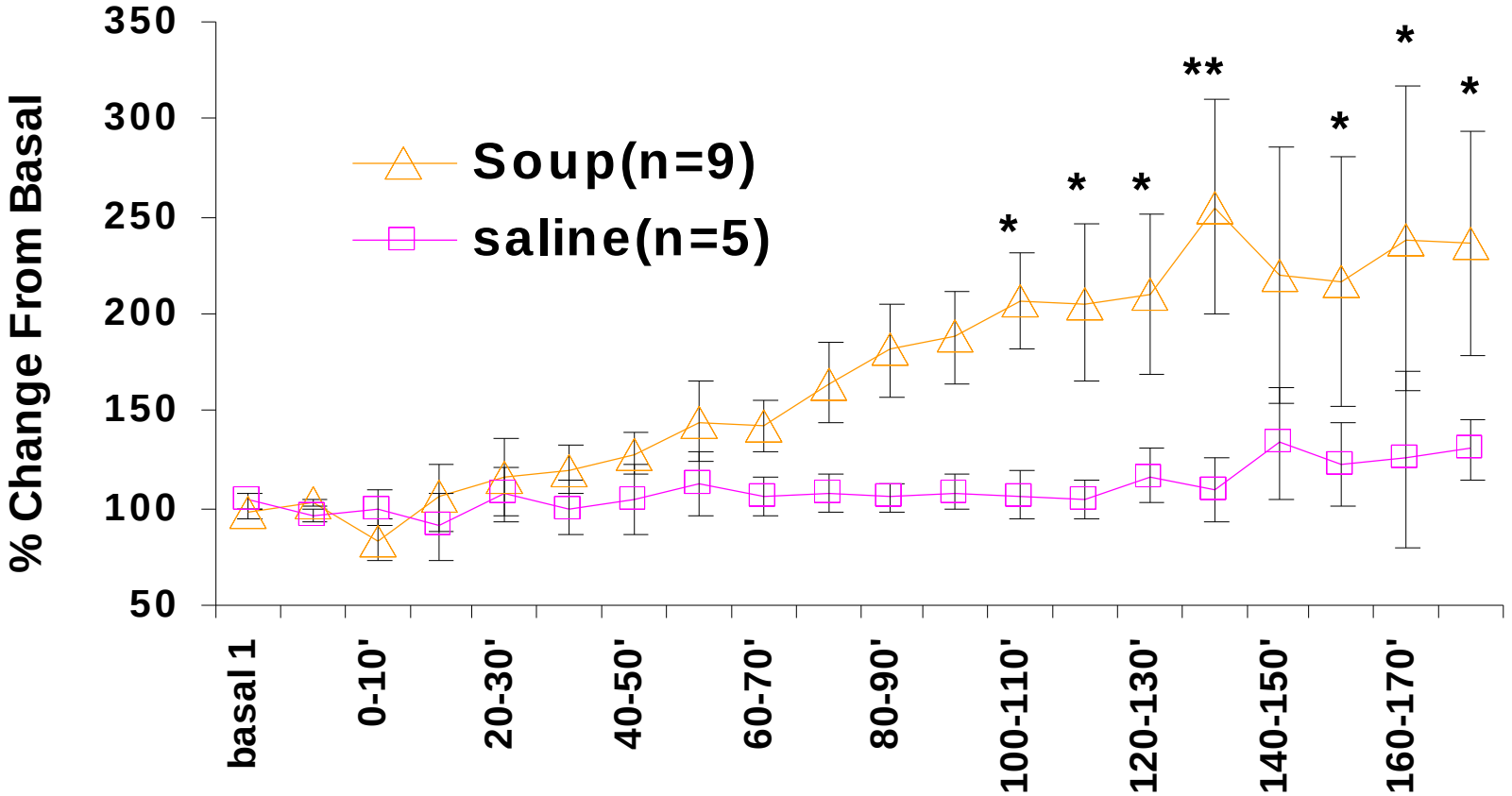




stimulus

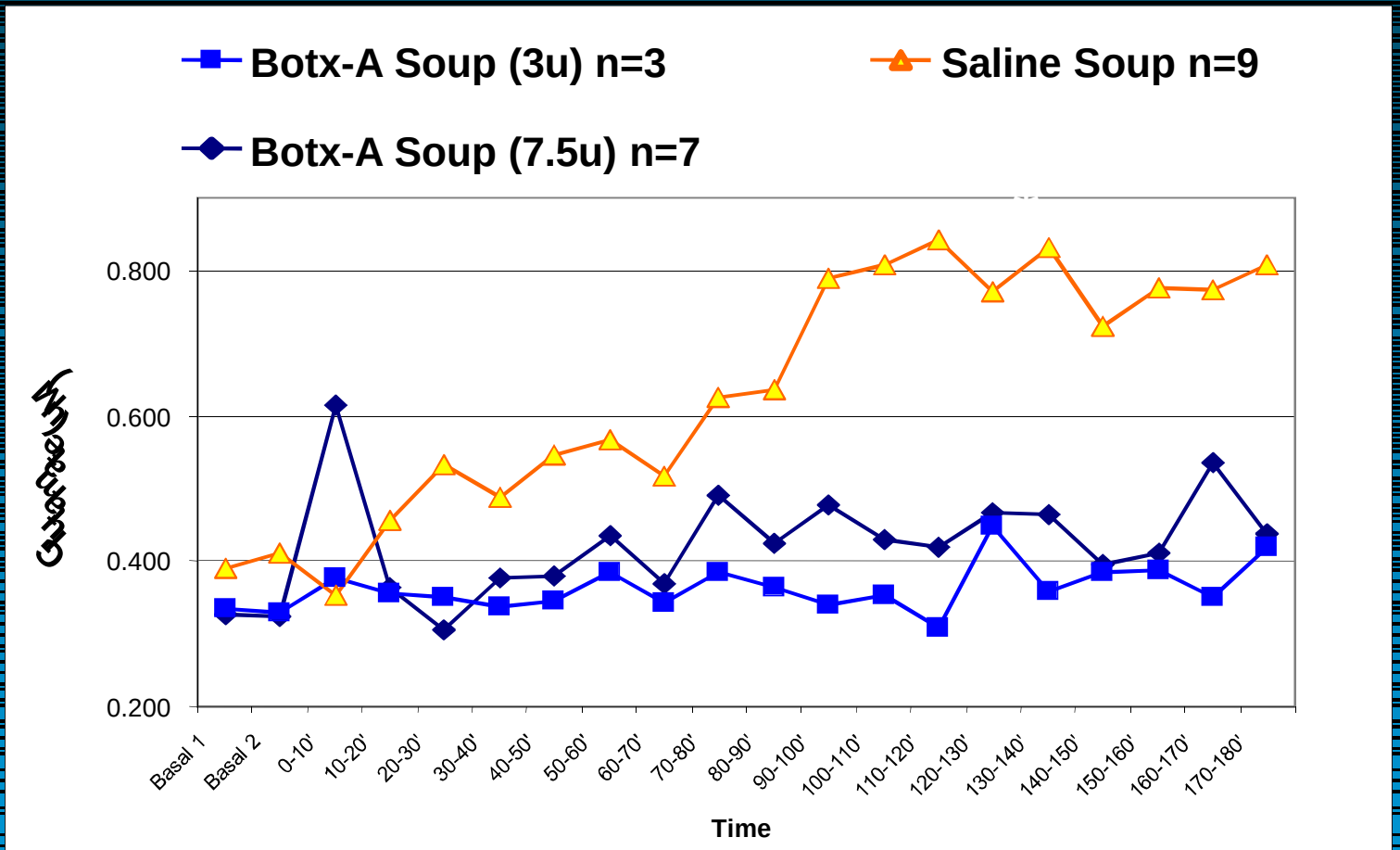
1 sec

# Inflammatory Soup Induced Extracellular Glutamate Change In The TNC




GLS random effects model * p<0.05, ** p<0.01

# Glutamate in the TNC



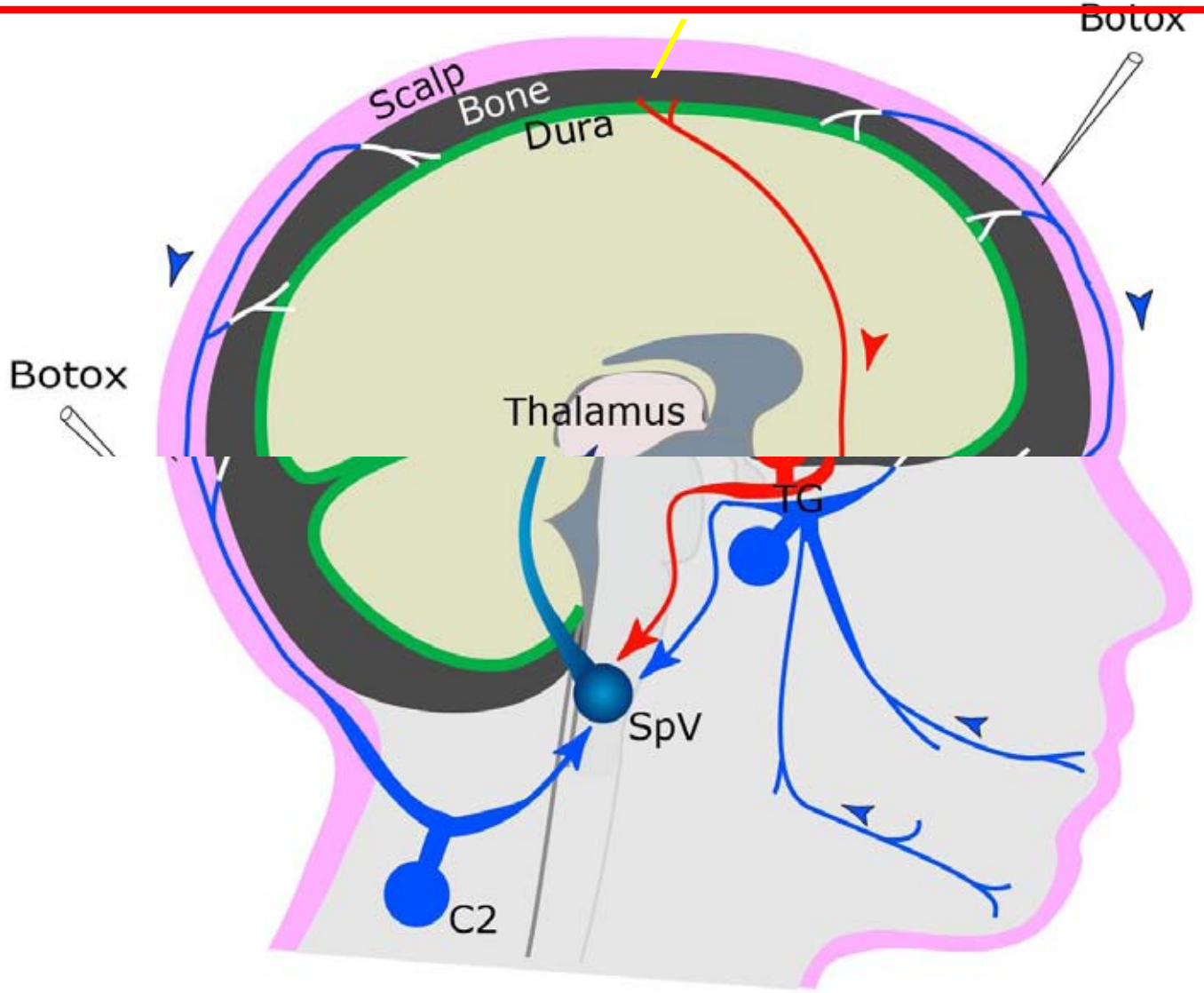



* GLM ANOVA p<0.01

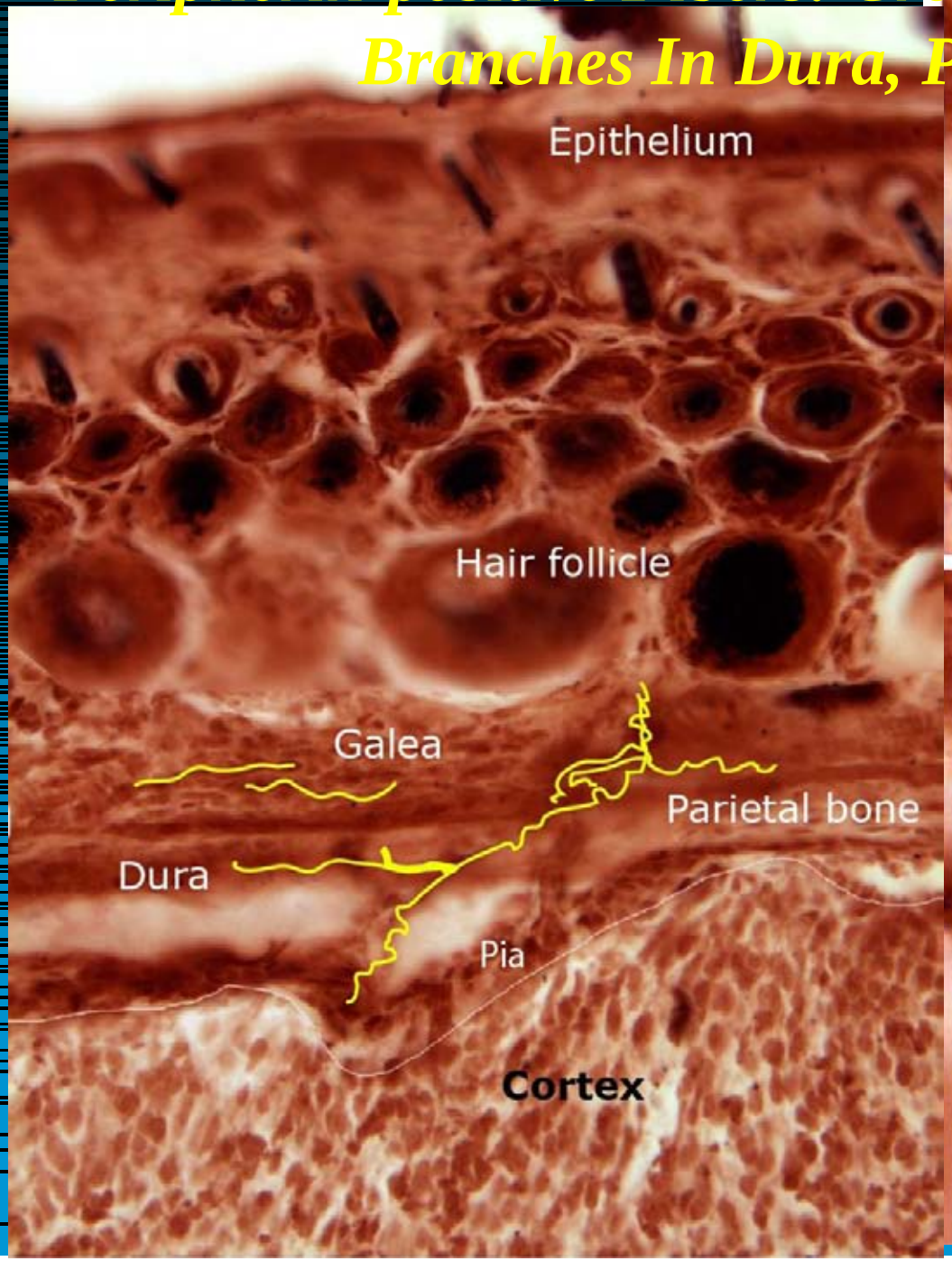
# *BTX-A Mechanism of Action*
## *When Injected in Forehead of Rats*

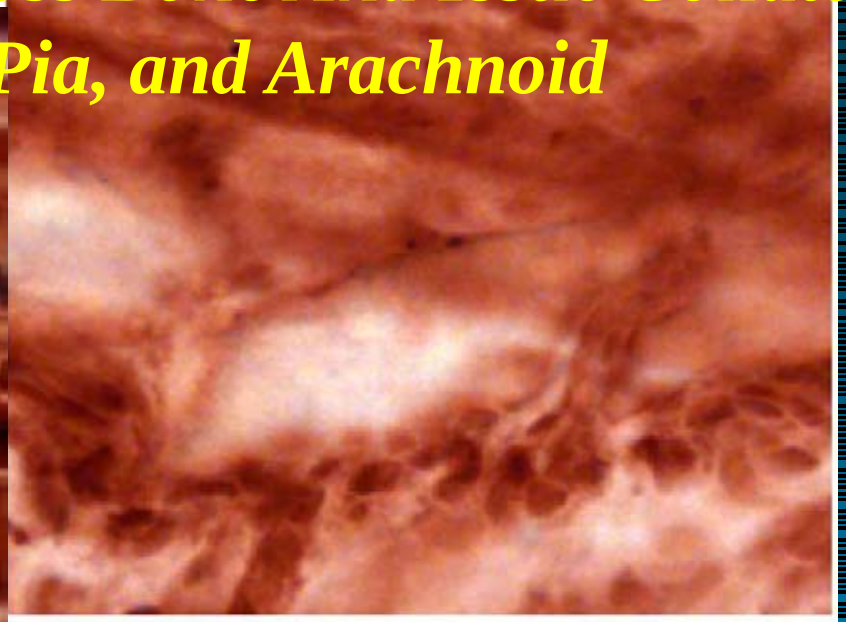
- TNC Neurons without dural receptive fields sensitize to inflammatory soup on dura
- BoTx-A blocks increase in response and receptive field following inflammatory soup
  - Inhibits peripheral sensitization by inhibiting local neurotransmitter release
  - Indirect reduction of central sensitization

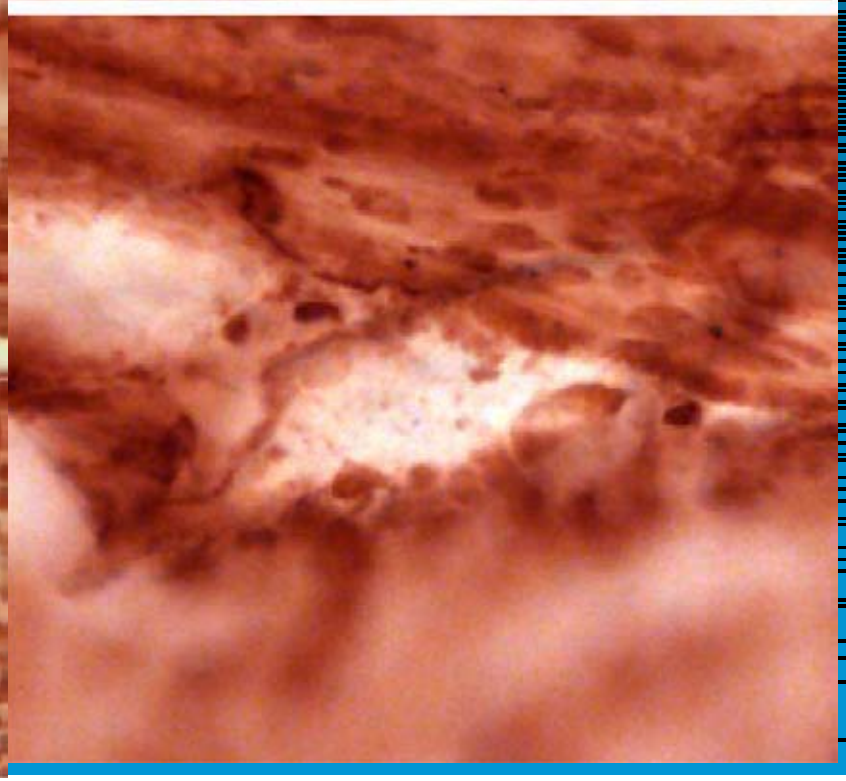
# *BTX-A Mechanism: Extracranial Injection of Collateral Branches?*



# *Peripherin-positive Fibers: Cross Bone And Issue Collateral Branches In Dura, Pia, and Arachnoid*





**Rami Burstein**

# *Response Properties, Trajectories And Anatomical Characterization Of Rat Trigeminal Calvarial Periosteal Afferents*

*Jun Zhao and Dan Levy*

1. Sensory innervation of calvarial periosteum is comprised primarily of small and medium size TG afferents with cell bodies in the V1 region
2. Most of the TG sensory innervation of the calvarial periosteum supplied by the supraorbital nerve.
3. Most calvarial periosteal afferents have characteristics of Mechano-nociceptors.
4. Calvarial periosteal afferents do not respond to CAP, most are poor acid sensors BUT many can be activated and sensitized by IM.
5. Inflammatory stimulation of calvarial periosteal afferents can lead to peri-orbital tactile hypersensitivity (central sensitization?)

# *BTX-A for Headache*

- Injection protocols
  - Fixed site
  - "Follow the pain"
  - Combination
- Optimal dosing and protocols evolved from initial "cosmetic pattern"

# *Silberstein et al 2006: Program to Assess Treatment Strategies (PATS)*

- Observational study from 10 US headache centers
- Online database of patient clinical data
- Patients (N = 703) aged 13-82 yr (mean, 42.7 yr); 78.5% female; 95.4% Caucasian
  - Moderate to severe headaches in 95.4% of patients
  - Moderate to severe disability in 79% of patients
  - > 90% failed previous prophylactic treatment
- Patients treated with BoNT-A in regular clinical practice

Silberstein SD, et al. Presented at 48th Annual Scientific Meeting of American Headache Society, 2006

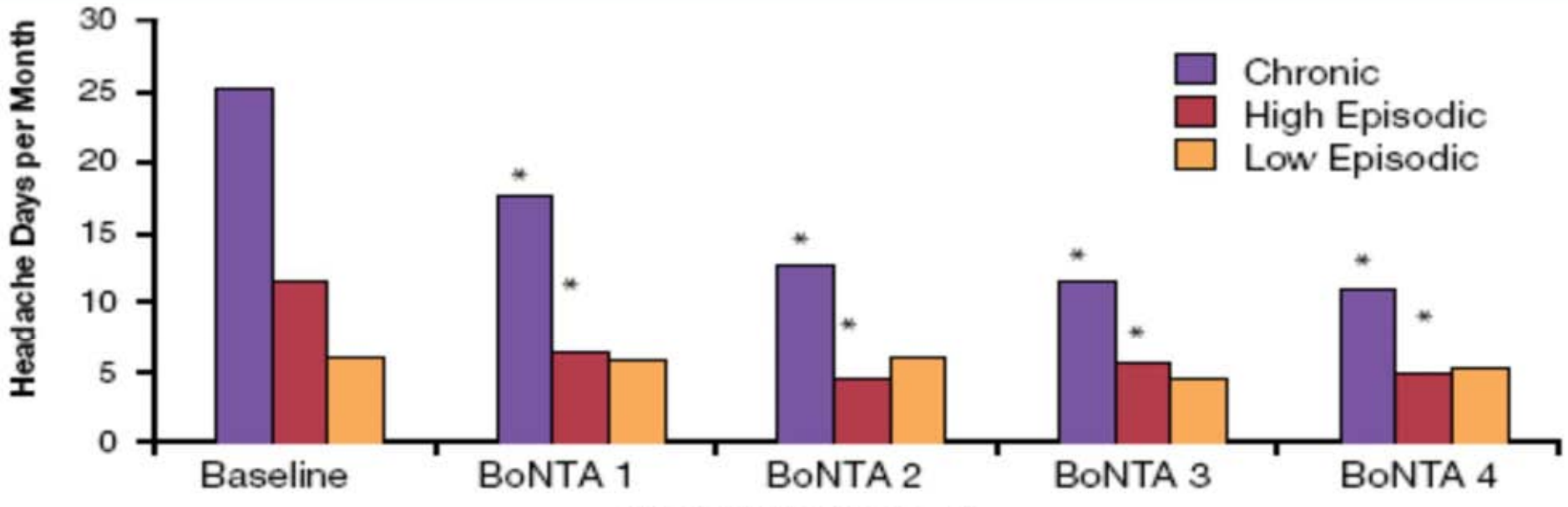
# *Silberstein et al 2006: Program to Assess Treatment Strategies (PATS)*

- 62.9% of patients and 65.8% of physicians reported improved headache symptoms
- Outcome
  - Mean MIDAS scores
    - Decreased from 71.1 (baseline) to 39.4
  - Mean number of headache days/3 mo
    - Decreased from 58.1 (baseline) to 37.8
- 482 (68.6%) continued BoNTA treatment at study end
- 0.4% (3/703) discontinued for AEs

Silberstein SD, et al. Presented at 48th Annual Scientific Meeting of the American Headache Society, 2006,

# *Silberstein et al 2006: Program to Assess Treatment Strategies (PATS)*

**Figure 1.** Headache frequency over time by baseline mean headache frequency.



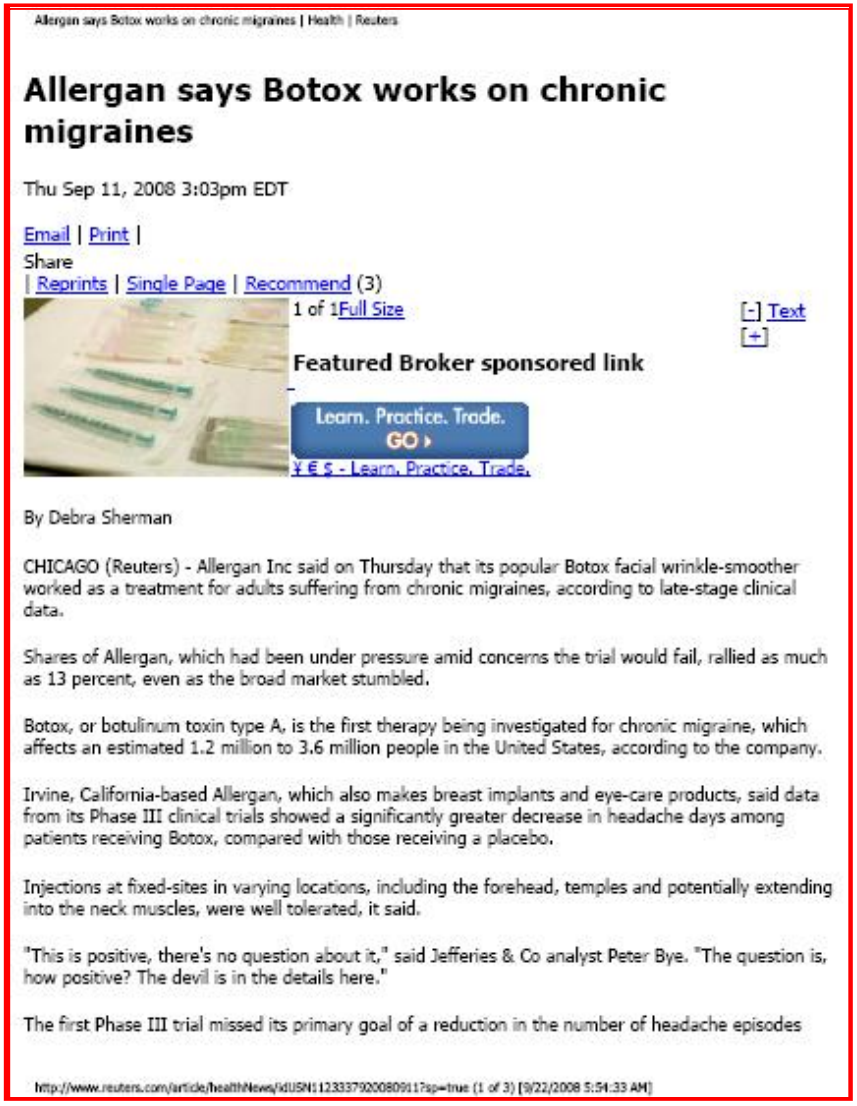

***Chronic ≥15***
***High episodic 10-14***
***Low episodic ≤9***

# *Silberstein et al 2006: Program to Assess Treatment Strategies (PATS)*

- Response greater in patients with CDH or high frequency episodic headaches (>9/month)
  - Mean headache severity significantly reduced in all groups
- Improvement in headache frequency regardless of concomitant headache prophylactic medications
- Headache diagnosis, use of headache prophylaxis, and dilution volume of BoNTA did not appear to predict treatment outcome

Silberstein SD, et al. Presented at 48th Annual Scientific Meeting of the American Headache Society, 2006

# *OnabotulinumtoxinA and CDH*



Allergan says Botox works on chronic migraines | Health | Reuters

**Allergan says Botox works on chronic migraines**

Thu Sep 11, 2008 3:03pm EDT

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By Debra Sherman

CHICAGO (Reuters) - Allergan Inc said on Thursday that its popular Botox facial wrinkle-smoother worked as a treatment for adults suffering from chronic migraines, according to late-stage clinical data.

Shares of Allergan, which had been under pressure amid concerns the trial would fail, rallied as much as 13 percent, even as the broad market stumbled.

Botox, or botulinum toxin type A, is the first therapy being investigated for chronic migraine, which affects an estimated 1.2 million to 3.6 million people in the United States, according to the company.

Irvine, California-based Allergan, which also makes breast implants and eye-care products, said data from its Phase III clinical trials showed a significantly greater decrease in headache days among patients receiving Botox, compared with those receiving a placebo.

Injections at fixed-sites in varying locations, including the forehead, temples and potentially extending into the neck muscles, were well tolerated, it said.

"This is positive, there's no question about it," said Jefferies & Co analyst Peter Bye. "The question is, how positive? The devil is in the details here."

The first Phase III trial missed its primary goal of a reduction in the number of headache episodes

http://www.reuters.com/article/healthNews/idUSN1233379200809l1?sp=true (1 of 3) [9/22/2008 5:54:33 AM]

- 2 D-B, P-C, trials
- Results published
  - Decrease in migraine days **P=0.006** and **p<0.001**
  - Decrease in migraine or probable migraine days **p=0.002** and **o<0.001**
- FDA approved for CM


# OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Results From the Double-Blind, Randomized, Placebo-Controlled PREEMPT Trials

David W Dodick[1]; Sheena K Aurora[2]; Catherine C Turkel[3]; Ronald E DeGryse[3]; Stephen D Silberstein[4]; Richard B Lipton[5]; Hans-Christoph Diener[6]; Mitchell F Brin[3,7]


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# *PREEMPT 1 and 2: Objective*

Evaluate efficacy and safety of OnabotulinumtoxinA (BOTOX®) for prophylaxis of headaches in adults with chronic migraine in two randomized, double-blind, placebo-controlled, parallel-group studies

# *PREEMPT 1 and 2 Study Design*

- Phase 3, 24-week, D-B, parallel, P-C, multicenter studies
  - 28-day baseline screening period (“baseline”)
  - 24-week, double-blind phase (2 injection cycles)
  - 32-week, open-label phase (3 injection cycles
- Study visits occurred every 4 weeks
- Patients recorded headache symptoms and acute headache medications in daily telephone diary
- Those overusing acute headache medications during baseline were designated as medication overuse (MO)



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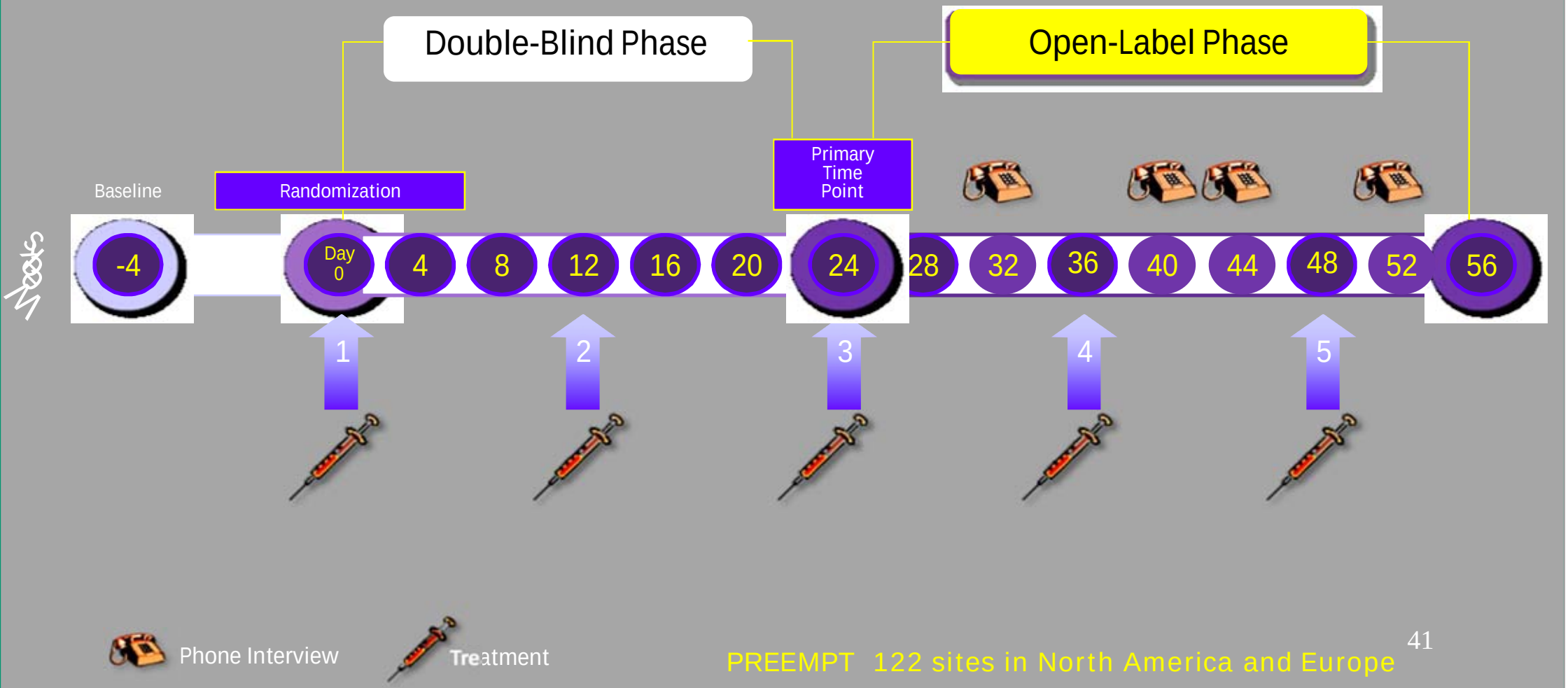
# PREEMPT Study Design




PREEMPT 122 sites in North America and Europe

OnabotulinumtoxinA 155 – 195 U (31 – 39 sites) or placebo

Dodick DW *et al. Headache* 2010;50:921–936.



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# *Principal Inclusion Criteria*

- Men or women aged 18 to 65 years
- History of migraine ICHD-II (2004), except complicated migraine.
- Headache occurring ?10 days/month, with each day consisting of ?4 hours of continuous headache
  - ?4 distinct headache episodes/month
  - ?50% of baseline headache days are migraine days*



*Migraine days or probable migraine days.

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# *Principal Exclusion Criteria*

- Any medical condition that might put patients at increased risk if exposed to onabotA
- Diagnosis of other primary/secondary headache disorder except MO
- Use of headache prophylactic medication within 28 days previous to start of baseline
- Beck Depression Inventory score >24
- Previous exposure to any botulinum toxin serotype



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# *Randomization and Study Treatment*

- Randomized (1:1) to onabotA (155 U) or placebo
- Stratified by baseline acute medication overuse (yes/no)
- Groups balanced within each medication overuse stratum for each investigator site
- Fixed-site, fixed-dose, Injections Q 12 weeks for 24 weeks
  - 2 cycles
  - 7 specific head/neck muscle areas; total 31 sites
- Option of additional onabotulinumtoxinA (up to 40 U)
  - 3 muscle groups (occipitalis, temporalis, or trapezius); total 8 sites
- Maximum dose: 195 U onabotA at 39 sites


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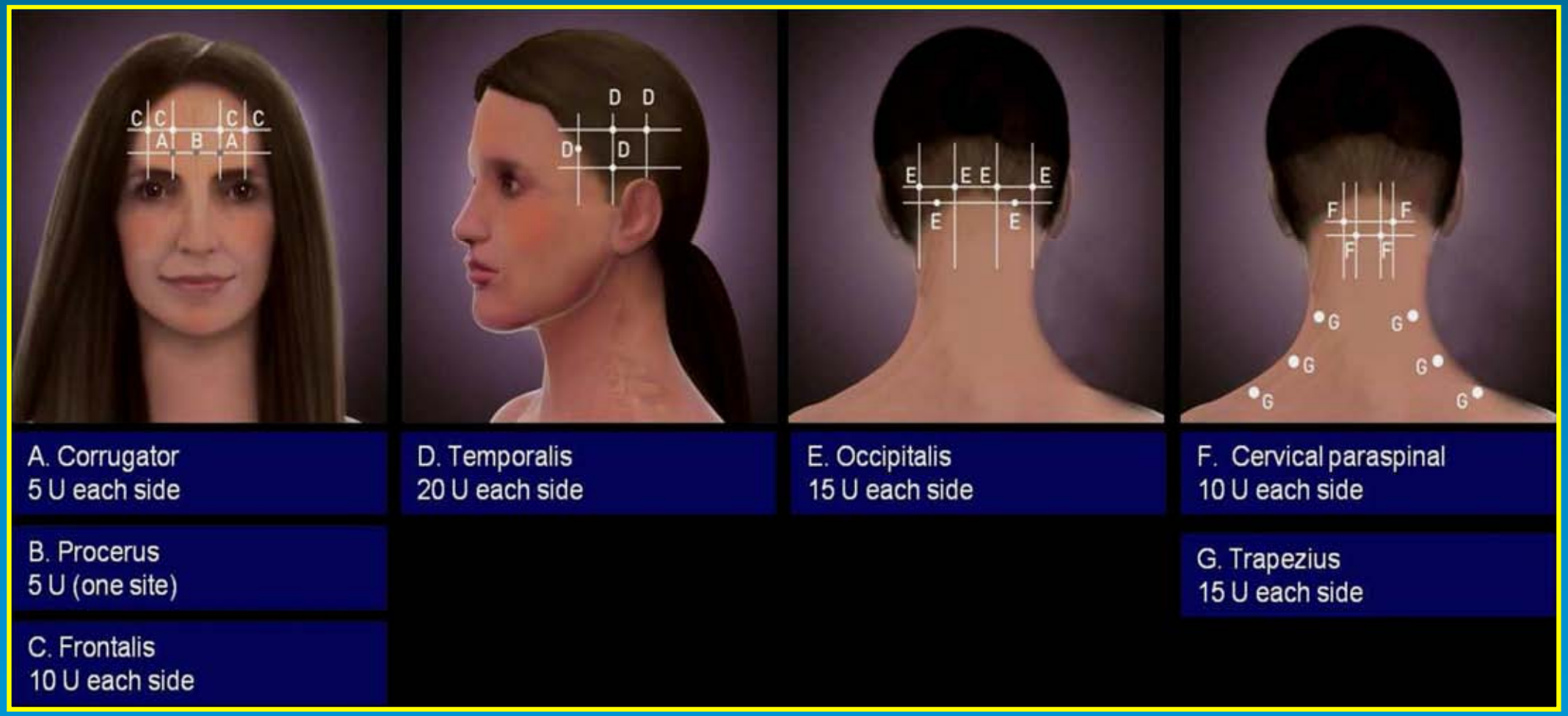
# *PREEMPT Injection Paradigm*

- Muscle groups 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 OnabotulinumtoxinA judgment of injector

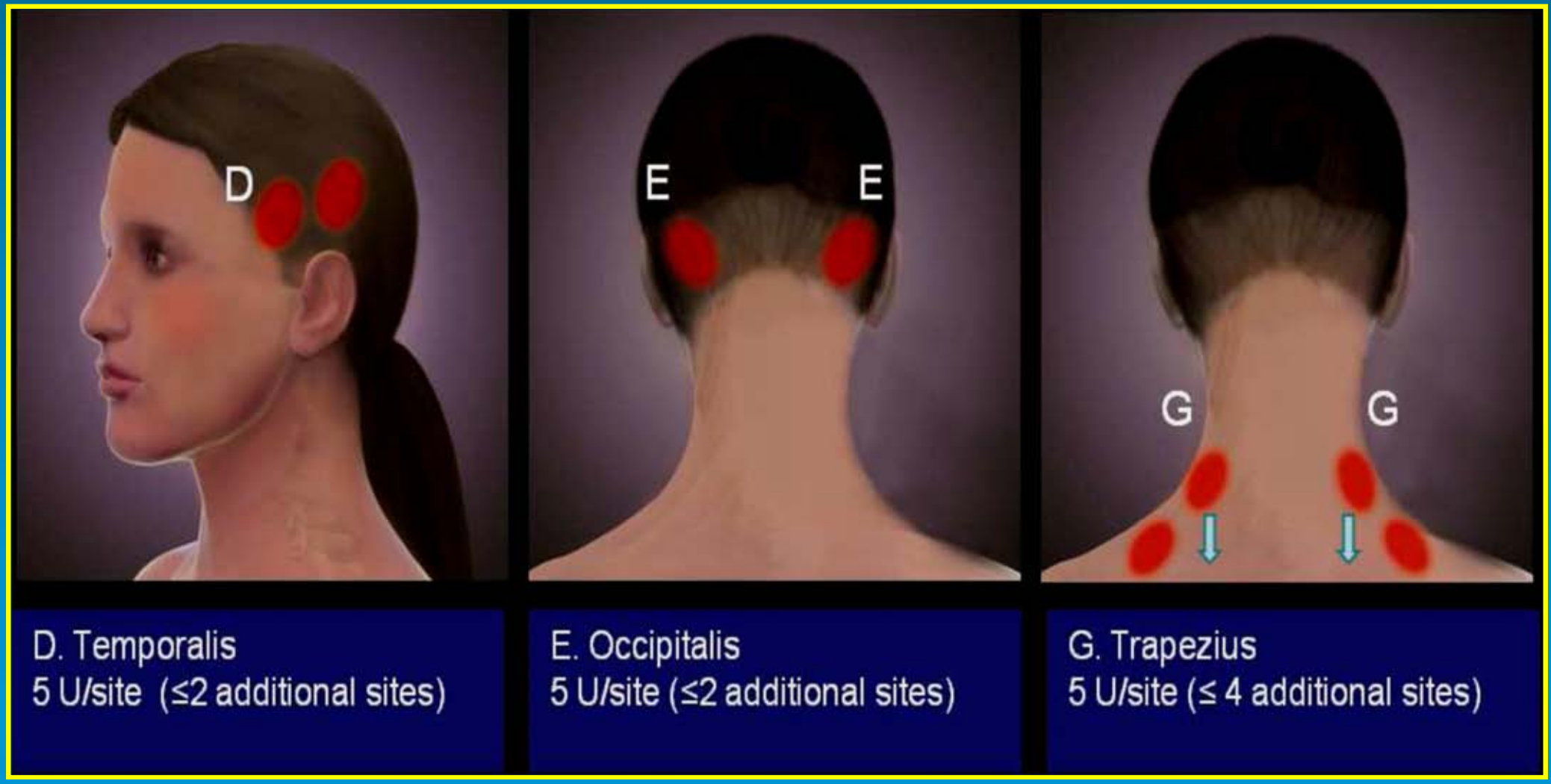
Blumenfeld AM *et al. Headache* 2010; In press.

# *Fixed-Site Fixed-Dose Injection Strategy*




- For each injection site, the injection volume is 0.1 mL (5 U)
- Each muscle has a fixed total dose, number and location of injection sites

# *Follow-The-Pain-Strategy*



# *Efficacy Endpoints*

**Change from 28-day baseline* to 28 days ending week 24 in:**

- MO-yes subgroup, primary variable frequency of headache days.
- Secondary variables included:
  - Frequency of migraine days
  - Frequency of moderate/severe headache days
  - Monthly cumulative headache hours on headache days
  - Frequency of headache episodes
  - Frequency of migraine episodes
  - Frequency of acute medication use
  - Proportion of patients with severe (?60) HIT-6 scores at week 24

HIT = Headache Impact Test.



***Randomized subjects provided diary data on ?20 of 28 days during the 28-day baseline.**

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# Pooled Baseline Demographics

| | BTX-A (n=688) | Placebo (n=696) |
|---|---|---|
| Mean age, years | 41 | 42 |
| Mean years since onset of CM | 19 | 19 |
| Female, % | 88 | 85 |
| Caucasian, % | 90 | 91 |
| | | |
| Mean migraine days (SD) | 19 (4) | 19 (4) |
| Mean moderate/severe HA days (SD) | 18 (4.1) | 18 (4.3) |
| | | |
| Mean HIT-6 score | 66 | 65 |
| % Patients with severe (≥60) HIT-6 score | 94 | 93 |
| Mean HA episodes (SD) | 12 (5)* | 13 (6)* |
| | | |
| % Patients overusing acute HA pain medication | 65 | 66 |

HA = headache; HIT = Headache Impact Test.

*$p<0.05$

Dodick DW *et al. Headache* 2010;50:921–936.

# *OnabotulinumtoxinA: Efficacy at Week 24 (Primary Time Point)*

| Endpoint, Mean Change From Baseline | BTX-A (n=688) | Placebo (n=696) | p-value |
|---|---|---|---|
| | | | |
| Frequency of migraine days | -8.2 | -6.2 | <0.001 |
| Frequency of moderate/severe HA days | -7.7 | -5.8 | <0.001 |
| | | | |
| % Patients with severe (?,60) HIT-6 score | 67.6 | 78.2 | <0.001 |
| | | | |
| Frequency of HA episodes | -5.2 | -4.9 | 0.009 |
| Frequency of migraine episodes | -4.9 | -4.5 | 0.004 |
| Frequency of acute HA pain medication intake (all categories) | -10.1 | -9.4 | 0.247 |
| Frequency of triptan use | -3.2 | -2.1 | <0.001 |

Onabot statistically significantly more effective than placebo in reducing mean frequency of headache days at every visit in D-B phase starting at irst post-treatment study visit (Week 4)
HA = headache; HIT = Headache Impact Test.

Dodick DW et al. Headache 2010;50:921–936.

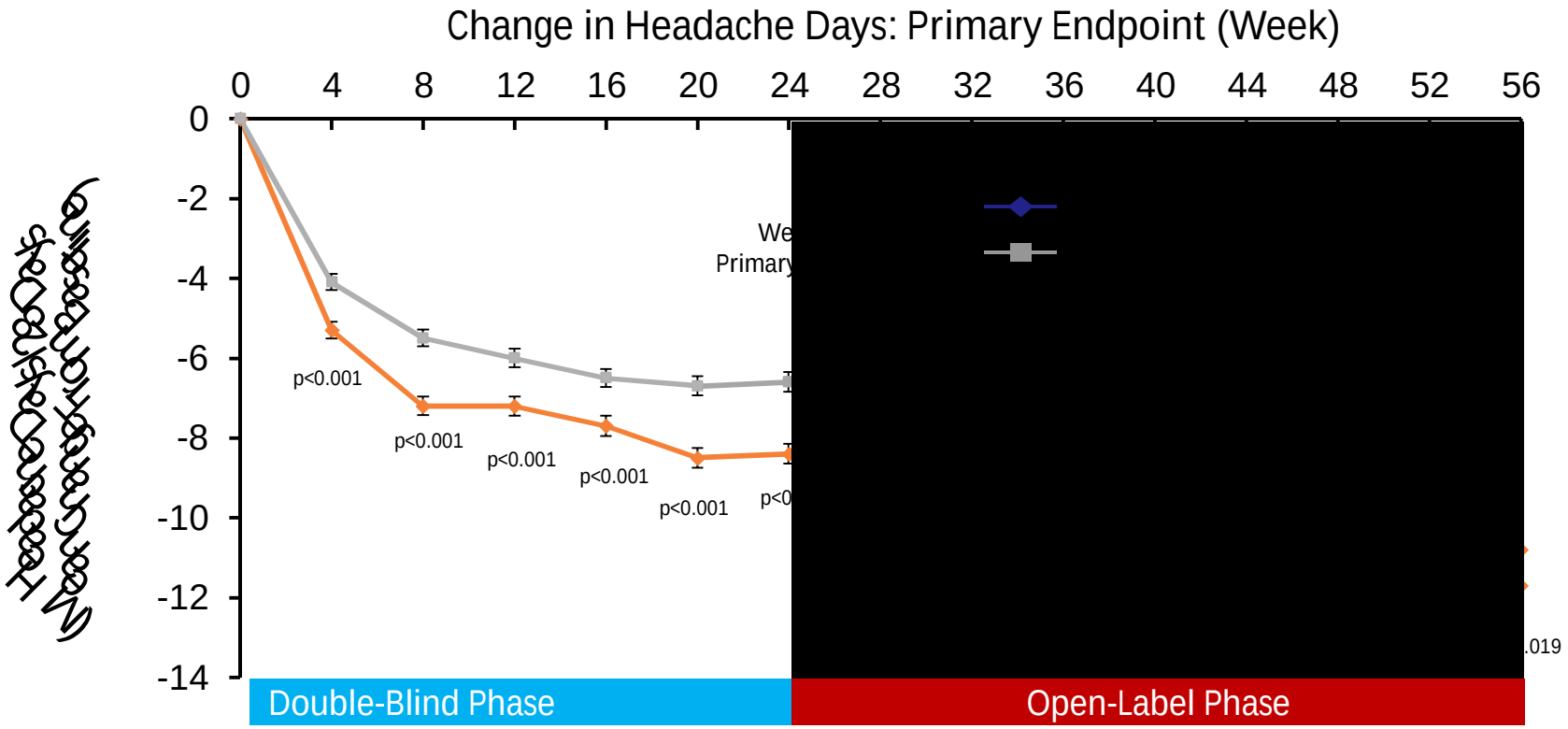
# Pooled Efficacy of BoNTA at Week 24 (Primary Time Point)

| Endpoint, Mean Change From Baseline | BoNTA (n=688) | Placebo (n=696) | p Value* |
|---|---|---|---|
| Frequency of HA days | -8.4 | -6.6 | <0.001 |
| Frequency of migraine days | -8.2 | -6.2 | <0.001 |
| Frequency of moderate/severe HA days | -7.7 | -5.8 | <0.001 |
| Total cumulative HA hours on HA days | -119.7 | -80.5 | <0.001 |
| % Patients with severe (?60) HIT-6 score | 67.6 | 78.2 | <0.001 |
| Total HIT-6 score | -4.8 | -2.4 | <0.001 |
| Frequency of HA episodes | -5.2 | -4.9 | 0.009 |
| Frequency of migraine episodes | -4.9 | -4.5 | 0.004 |
| Frequency of acute HA pain medication intake (all categories) | -10.1 | -9.4 | 0.247 |
| Frequency of triptan use | -3.2 | -2.1 | <0.001 |

**BoNTA statistically significantly more effective than placebo in reducing mean frequency of headache days at every visit in the double-blind phase starting at first post-treatment study visit (Week 4)**

Dodick DW *et al*. *Headache* 2010;50:921–936.

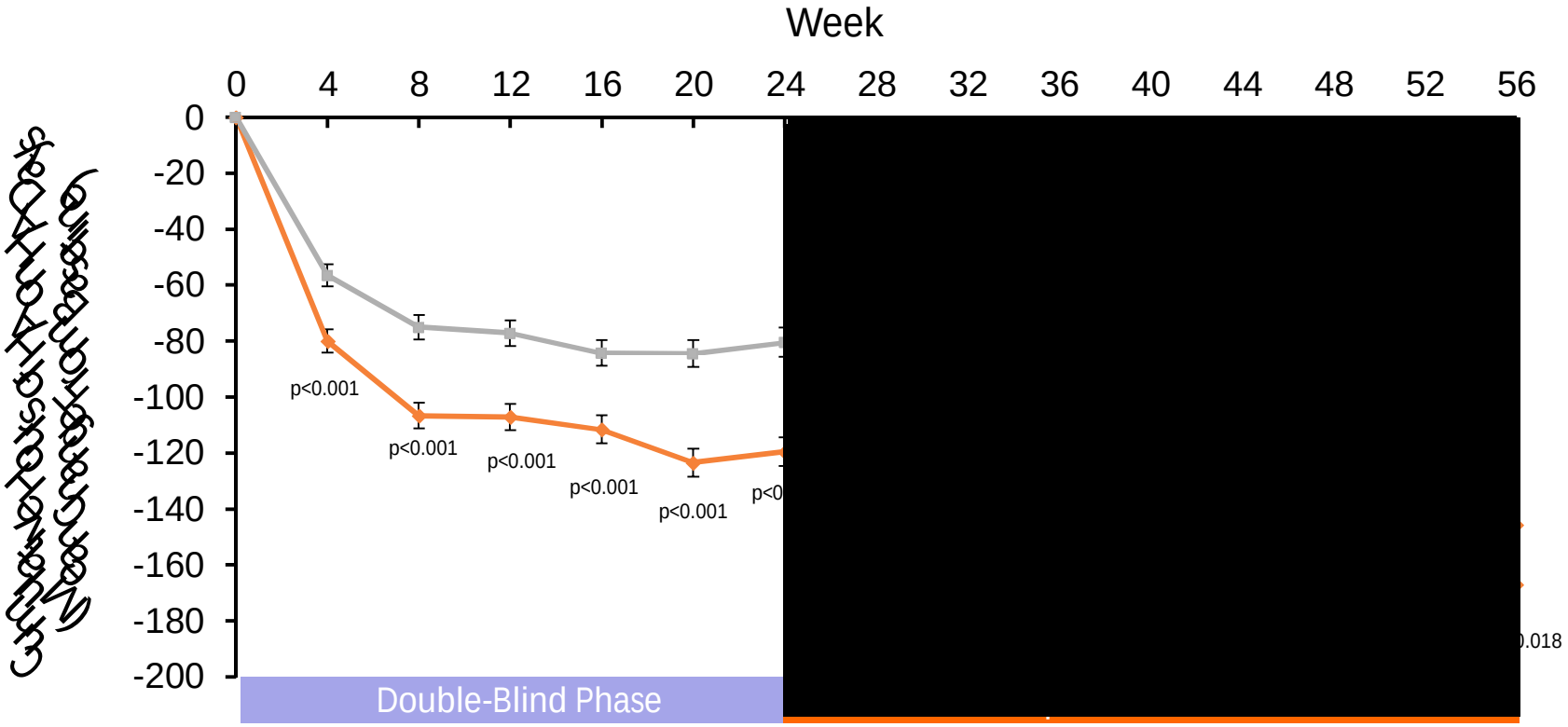
# *PREEMPT Pooled Analysis: ~70% of Patients Achieved ?50% Reduction in Headache Days at 56 Weeks*




*Patients who received BoNTA (Allergan) throughout the 56-week treatment programme.
Mean ± standard error.
The double-blind phase included 688 subjects in the BoNTA (Allergan) group and 696 in the placebo group.
Headache days at baseline: 19.9 BoNTA (Allergan) group vs 19.8 placebo group, p=0.498.
PREEMPT: Phase III Research Evaluating Migraine Prophylaxis Therapy.

Aurora SK *et al. Headache* 2011;51:1358–1373.

# PREEMPT Pooled Analysis: BoNTA (Allergan) Reduced Cumulative Headache Hours on Headache Days




Mean ± standard error.
The double-blind phase included 688 subjects in the BoNTA (Allergan) group and 696 in the placebo group.
Cumulative hours of headache at baseline: 295.9 BoNTA (Allergan) group vs 281.2 placebo group, p=0.021.
HA : Headache; PREEMPT: Phase III Research Evaluating Migraine Prophylaxis Therapy.

Aurora SK *et al. Headache* 2011;51:1358–1373.

# *PREEMPT Population Representative of Typical CM Sufferers Seen in General Population*

| | PREEMPT (n=1384) | AMPP* (n=655) |
|---|---|---|
| Mean age, years | 41.3 | 47.7 |
| Female, % | 86.4 | 78.6 |
| Caucasian, % | 90.1 | 90.7 |
| Body mass index | 27.0 | 29.8 |
| Acute medication (any use), % | 97.5 | 630 (96.2) |
| % Patients with severe (≥ 60) HIT-6 score | 93.1 | 72.9 |

*Data from 2005 American Migraine Prevalence Prevention survey.

Lipton RB et al. Presented at AHS 2010.

# *Open Label Long Term Extension*

- All received onabotA from 28 to 56-weeks
- Both groups continued to improve
  - Former placebo group never caught up
  - Significant improvements versus placebo
- OnabotA patients had reduced disease burden, improved functioning, vitality, psychological distress, and overall HRQoL
- Repeated treatment up to 5 cycles onabotA (155 to 195 U) every 12 weeks over 56 weeks safe and well tolerated



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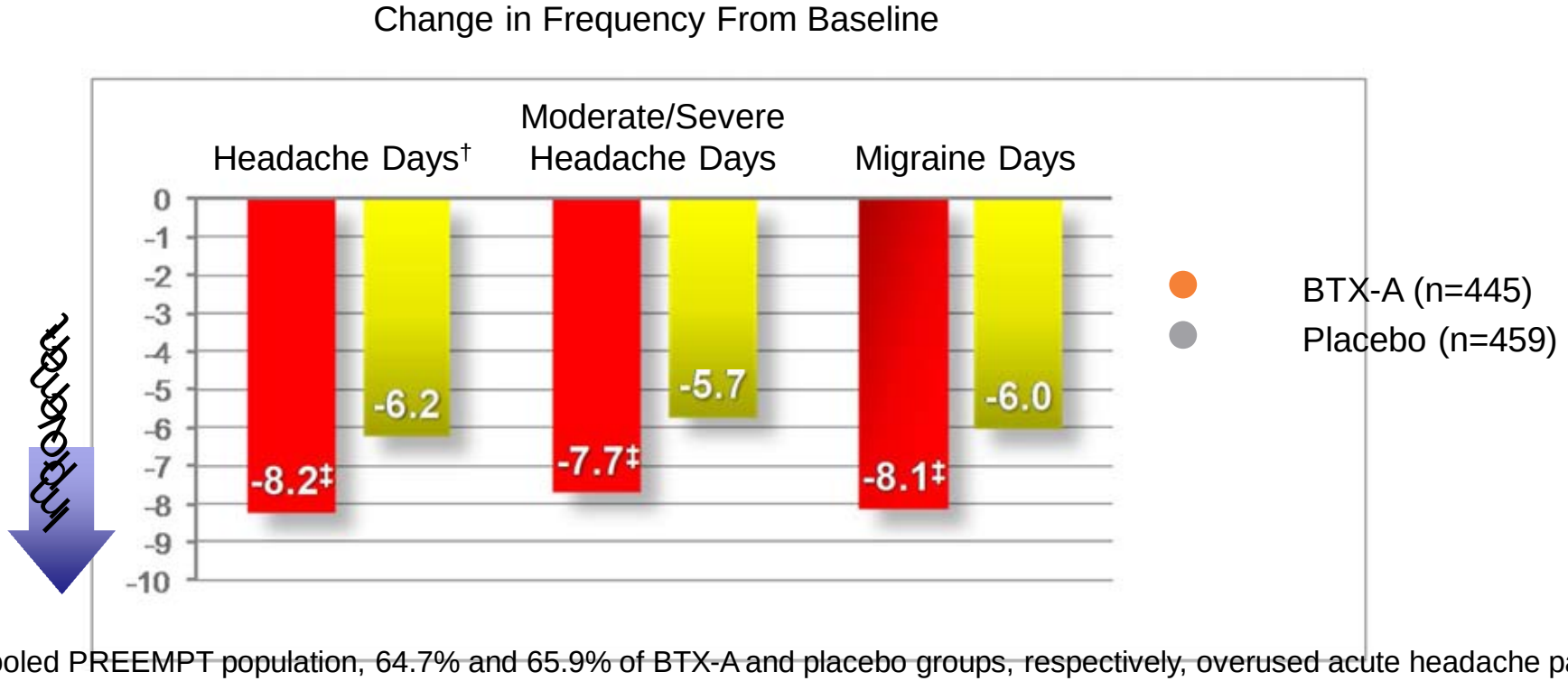
# *PREEMPT Pooled Analysis: Effective Treatment for CM Patients With Acute Pain Medications Overuse*

## Efficacy of BTX-A in Medication Overuse Subgroup* at Week 24




*Of the total pooled PREEMPT population, 64.7% and 65.9% of BTX-A and placebo groups, respectively, overused acute headache pain medication (simple analgesics, ergotamine/DHE, triptans, opioids, combination analgesics, or any combination of the preceding classes).

†Headache days are reported as headache days per 28 days; change in frequency of headache days was the primary endpoint of the pooled analysis.

‡$p<0.001$.

Silberstein SD *et al.* Presented at IHC 2009.

# *CM With MO: Conclusions*

## OnabotulinumtoxinA

- Highly significant improvements versus placebo in subgroup overusing acute headache medication at baseline
  - Significantly reduced headache-related disability, and improved functioning and overall QoL
- Effective, safe, and well-tolerated treatment for CM in patients overusing acute headache medications during 28-day baseline



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# *Headache Impact Test (HIT)-6**
# *Validated headache-specific quality-of-life measure*

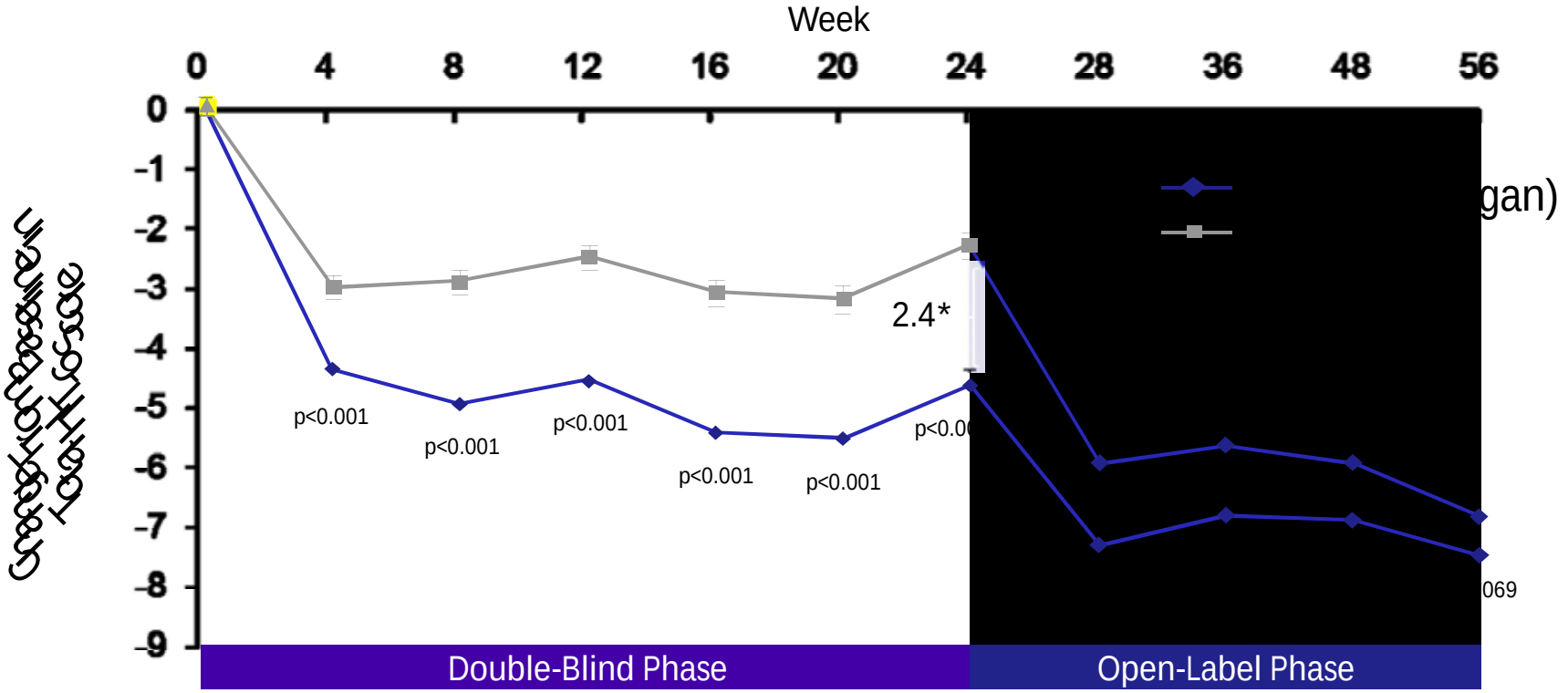
**Captures 6 criteria: Degree of pain, role functioning, social functioning, vitality, cognitive functioning, and psychological distress[1]**

**Each question scored: Never (6), Rarely (8), Sometimes (10), Very Often (11), or Frequently (13), for a total score ranging from 36 to 78**

| | |
|---|---|
| **1.** | When you have headaches, how often is the pain severe? |
| **2.** | How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities? |
| **3.** | When you have a headache, how often do you wish you could lie down? |
| **4.** | In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches? |
| **5.** | In the past 4 weeks, how often have you felt fed up or irritated because of your headaches? |
| **6.** | In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities? |

1. Kosinski M *et al. Qual Life Res* 2003;12:963–974.
2. HIT-6 Questionnaire version 1.1. http://www.headachetest.com/HIT6/PDFS/English.pdf. Accessed June 7, 2011.

# PREEMPT Pooled Analysis: Mean Total HIT-6 Scores: HRQoL Improved With BoNTA (Allergan)[1]




*Between-group difference exceeded the minimally important difference (MID) for HIT-6 (2.3 units)[2] indicating a clinically significant effect of BoNTA (Allergan) treatment.

The double-blind phase included 688 subjects in the BoNTA (Allergan) group and 696 in the placebo group.
Total HIT-6 scores at baseline: 65.5 BoNTA (Allergan) group vs 65.4 placebo group; p=0.638.
HIT: Headache Impact Test; HRQoL: Health-related quality of life; PREEMPT: Phase III Research Evaluating Migraine Prophylaxis Therapy.


1. Lipton RB *et al.* Presented at AAN 2010.
2. Coeytaux RR *et al.* *J Clin Epidemiol* 2006;59:374–380.

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

| | BoNTA (Allergan) (n=687) | Placebo (n=692) |
|---|---|---|
| All adverse events (AEs)* | 62.4 | 51.7 |
| Treatment-related AEs† | 29.4 | 12.7 |
| Serious AEs | 4.8 | 2.3 |
| Treatment-related, serious AEs† | 0.1‡ | 0.0 |
| Discontinuations related to AEs§ | 3.8 | 1.2 |
| Deaths | 0.0 | 0.0 |

*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.
‡Migraine requiring hospitalisation.
§The most frequently reported AEs leading to discontinuation in the BoNTA (Allergan) group were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%).
PREEMPT: Phase III Research Evaluating Migraine Prophylaxis Therapy.

Dodick DW *et al. Headache* 2010;50:921–936.

# *PREEMPT: Summary of Adverse Events Pooled Data, Double-Blind Phase (%)*

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| Discontinuations related to AEs§ | 3.8 | 1.2 |
| Deaths | 0.0 | 0.0 |

***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.**
**‡Migraine requiring hospitalization.**
**§The most frequently reported AEs leading to discontinuation in the BOTOX® group were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%).**

Dodick DW *et al*. *Headache* 2010;50:921–936.

# PREEMPT: Treatment-Related AEs in ?Æ2% Patients Pooled Data, Double-Blind Phase (%)

**Only neck pain and muscular weakness were reported in ?5% of patients**

| | BTX-A (n=687) | Placebo (n=692) |
|---|---|---|
| Total treatment-related AEs | 29.4 | 12.7 |
| Neck pain | 6.7 | 2.2 |
| Muscular weakness | 5.5 | 0.3 |
| Eyelid ptosis | 3.3 | 0.3 |
| Injection-site pain | 3.2 | 2.0 |
| Headache | 2.9 | 1.6 |
| Myalgia | 2.6 | 0.3 |
| Musculoskeletal stiffness | 2.3 | 0.7 |
| Musculoskeletal pain | 2.2 | 0.7 |

**Most AEs were mild or moderate in severity and resolved without sequelae.**

Dodick DW *et al. Headache* 2010;50:921–936.

# *PREEMPT Injection Paradigm*

- Fixed-site, fixed-dose and modified follow-the-pain treatment
  - 155 U of OnabotA administered as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas
- Up to 40 U can be administered at additional 8 sites at physician's discretion using a modified follow-the-pain strategy for a maximum dose of 195 U
- **Dosing**
  - For each injection site, the injection volume is .1 mL (5 U)
  - Each muscle has a fixed:
    - Total dose
    - Number of injection sites
    - Location of injection sites

# *PREEMPT Injection Paradigm*

- Revised  muscle groups injections from preceding phase 2 trials*
- Paradigm includes  fixed-site, fixed-dose and modified follow-the-pain treatment
  - 155 U of OnabotA  administered as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas
- Up to 40 U of additional OnabotA can be administered at additional 8 sites at physician's discretion using a modified follow-the-pain strategy for a maximum dose of 195 U
- **Dosing**
  - For each injection site, the injection volume is .1 mL (5 U)
  - Each muscle has a fixed:
    - Total dose
    - Number of injection sites
    - Location of injection sites

# *BoNTA (Allergan) Reconstitution and Dilution*

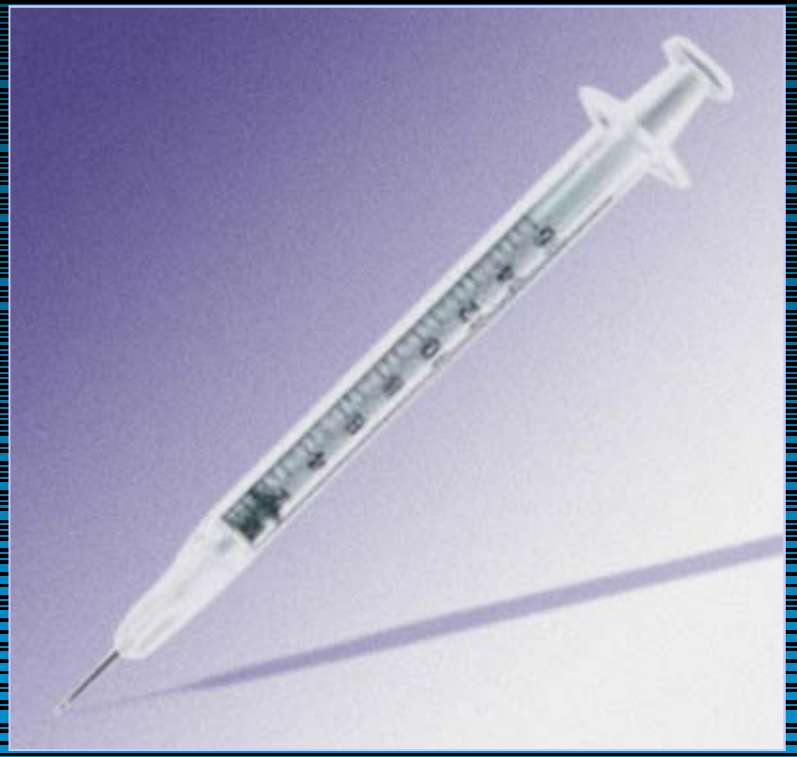
| Dilution Recommendation | |
|---|---|
| **Saline added (0.9% sodium chloride injection)** | **Resulting BoNTA (Allergan) dose (U per 0.1 mL)** |
| | |
| | |
| | |
| | |

Resulting concentration is 5 U per 0.1 mL

Once reconstituted, BoNTA (Allergan) must be injected or immediately stored at 2°C to 8°C

# *Injection Technique Considerations*

- Needle size
  - 30-gauge with tuberculin syringe **Luer lock**
- Angle of needle
  - Site- and operator-dependent
- Patient position
  - Sitting or lying down
- Dilute 100 U BoNTA
  - With 2 mL sterile normal saline



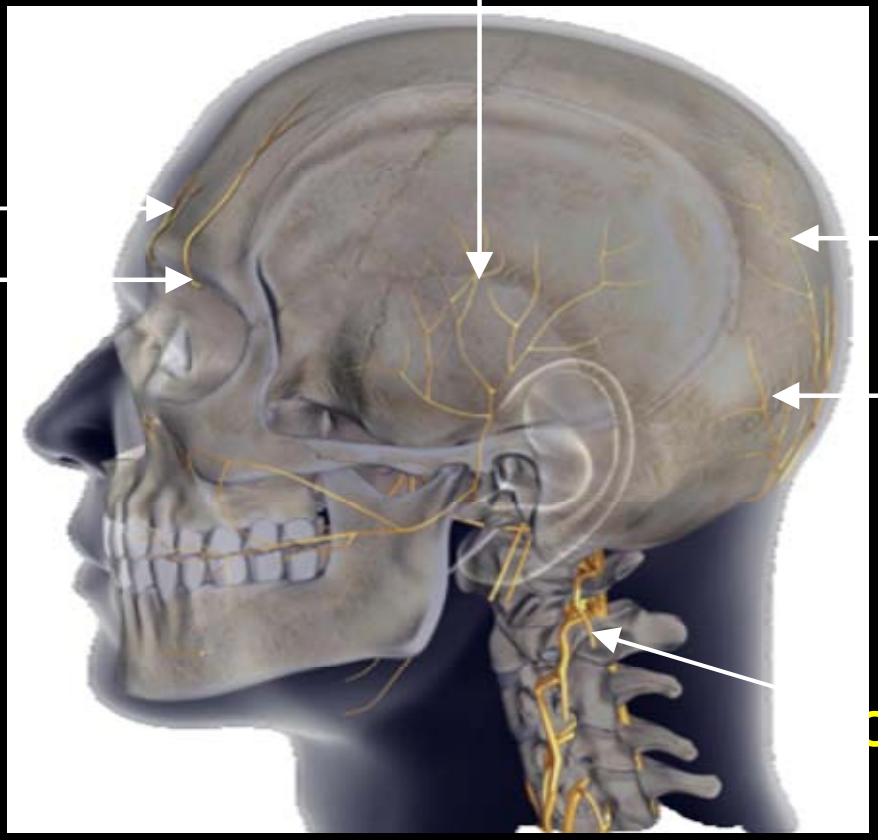
# *Injection Paradigm: Required Dose Using a Fixed-Site, Fixed-Dose Paradigm*

| Order | Muscle | Number of Units (U) |
|---|---|---|
| A | Corrugator | 10 (5 each side) |
| B | Procerus | 5 |
| C | Frontalis | 20 (10 each side) |
| D | Temporalis | 40 (20 each side) |
| E | Occipitalis | 30 (15 each side) |
| F | Cervical paraspinal | 20 (10 each side) |
| G | Trapezius | 30 (15 each side) |
| **Total number of units (U)** | | **155** |

# *CM PREEMPT Follow-the-Pain Injection Paradigm*

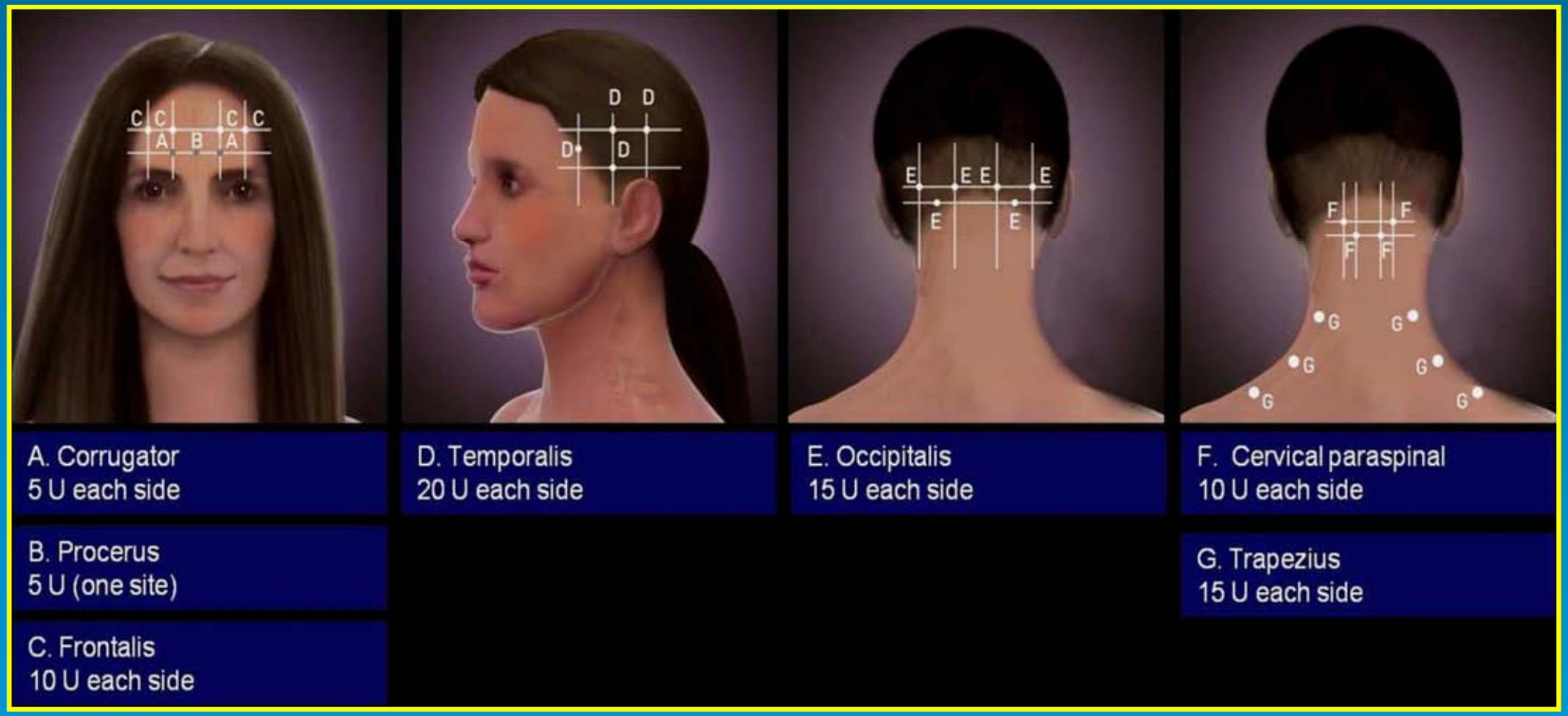
| Order | Muscle | Number of Units (U)* | | Additional Units (U), if necessary |
|---|---|---|---|---|
| **A** | Corrugator† | 10 (5 each side) | | **NA** |
| **B** | Procerus | 5 | | **NA** |
| **C** | Frontalis† | 20 (10 each side) | | **NA** |
| **D** | Temporalis† | 40 (20 each side) | **+** | **10 (up to 2 sites)** |
| **E** | Occipitalis† | 30 (15 each side) | **+** | **10 (up to 2 sites)** |
| **F** | Cervical paraspinal† | 20 (10 each side) | | **NA** |
| **G** | Trapezius† | 30 (15 each side) | **+** | **20 (up to 4 sites)** |
| **Total number of units (U)** | | **155** | **to** | **195** |

# *Anatomical Injection Sites Follow Areas Innervated by the Trigeminal Sensory System*



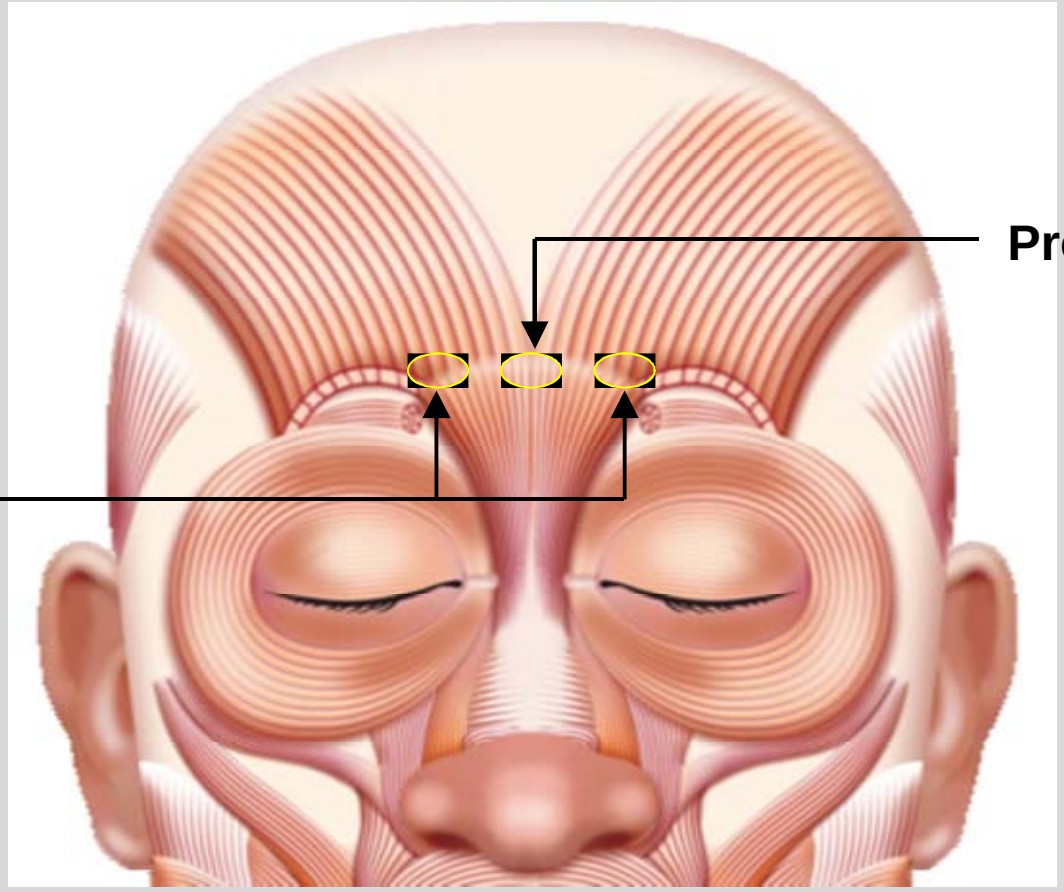

Schuenke M *et al.*, eds. *Theime Atlas of Anatomy: Head and Neuroanatomy*. Stuttgart: Thieme; 2010.

# *Fixed-Site Fixed-Dose Injection Strategy*




- For each injection site, the injection volume is 0.1 mL (5 U)
- Each muscle has a fixed total dose, number and location of injection sites

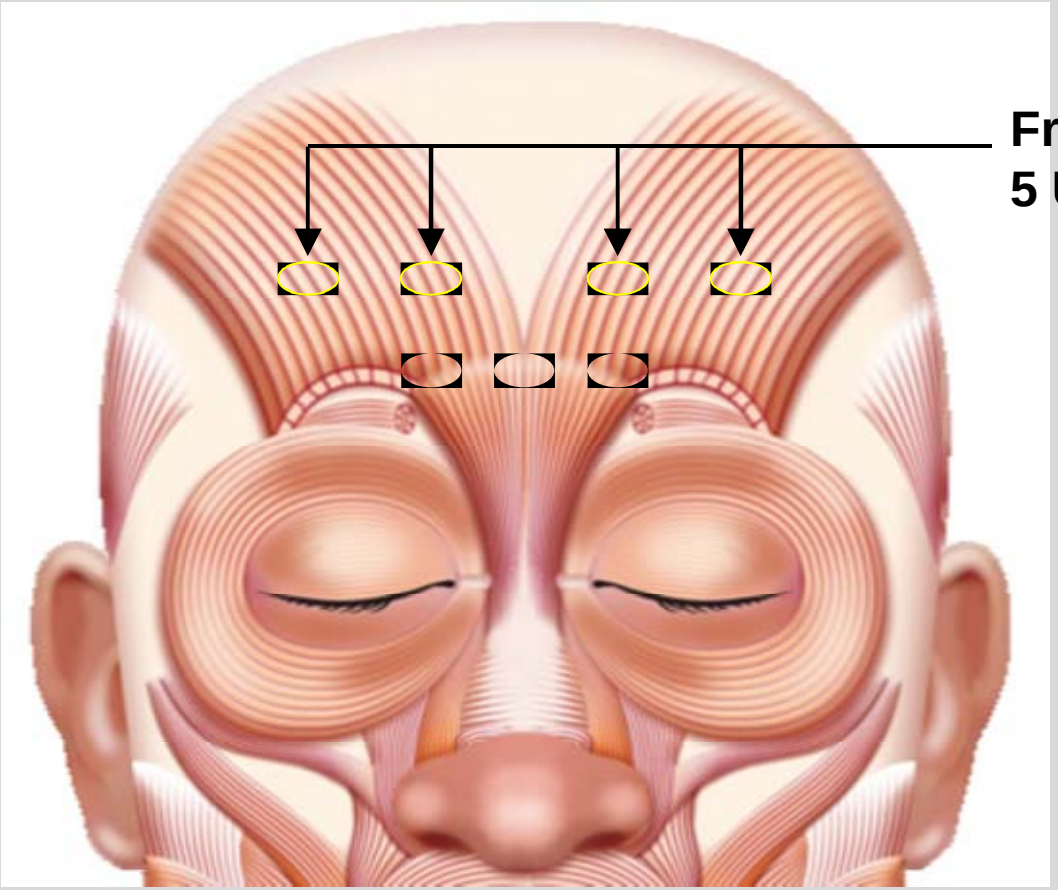
# *Injection Sites: Corrugator and Procerus*




**Patient position:** Supine[1]

**Dose:** 3 injections of 0.1 mL (a total of 15 U divided into 3 sites)[1]

# *Injection Site: Frontalis*



**Frontalis:**
**5 U at each site[1]**

**Patient position:** Supine[1]

**Dose:** 2 injections of 0.1 mL on each side (a total of 20 U divided into 4 sites)[1]

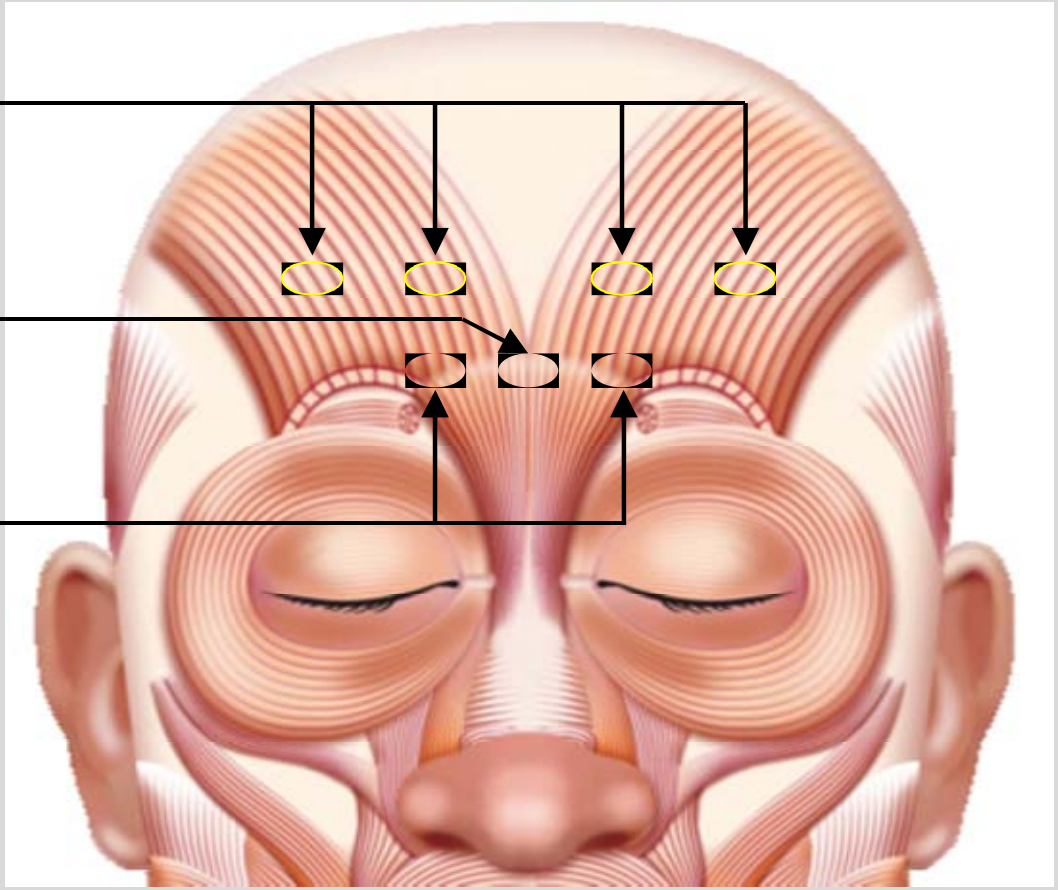
**1.** Blumenfeld AM *et al. Headache* 2010;**50**:1406–18.

# *Injection Sites: Corrugator, Procerus and Frontalis*

**Frontalis:**
**4 x 5 U[1]**

**Procerus:**
**1 x 5 U[1]**

**Corrugator:**
**2 x 5 U[1]**

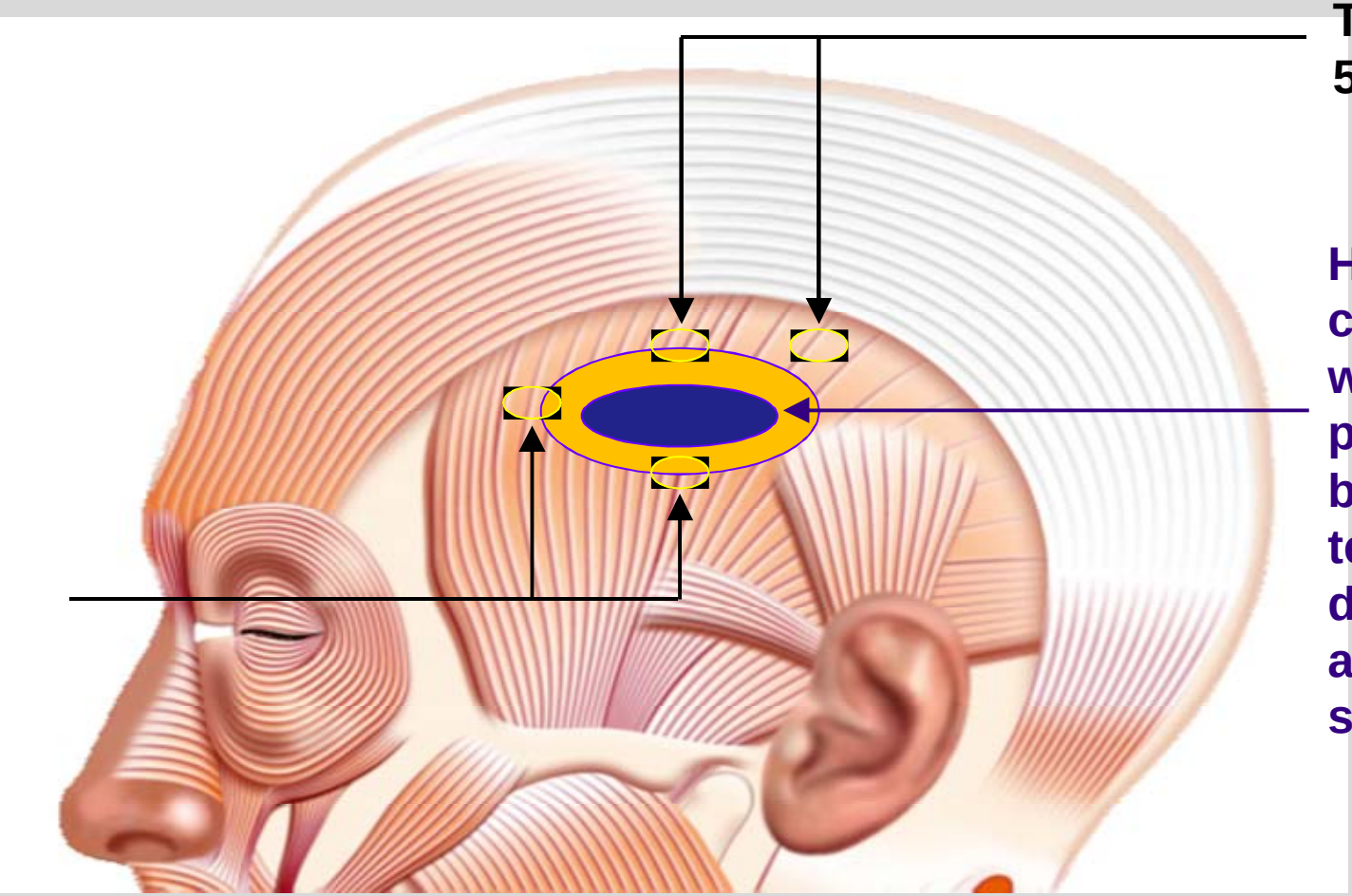


**Patient position:** Supine[1]

**Dose:** 7 injections of 0.1 mL (a total of 35 U divided into 7 sites)[1]

1. Blumenfeld AM *et al. Headache* 2010;**50**:1406–18.

# *Injection Site: Temporalis*



**Temporalis: 5 U at each site[1]**

**Temporalis: 5 U at each site[1]**

**Having the patient clench their teeth will produce a palpable anterior bulge to the temporalis muscle, directing the anterior injection site[1]**

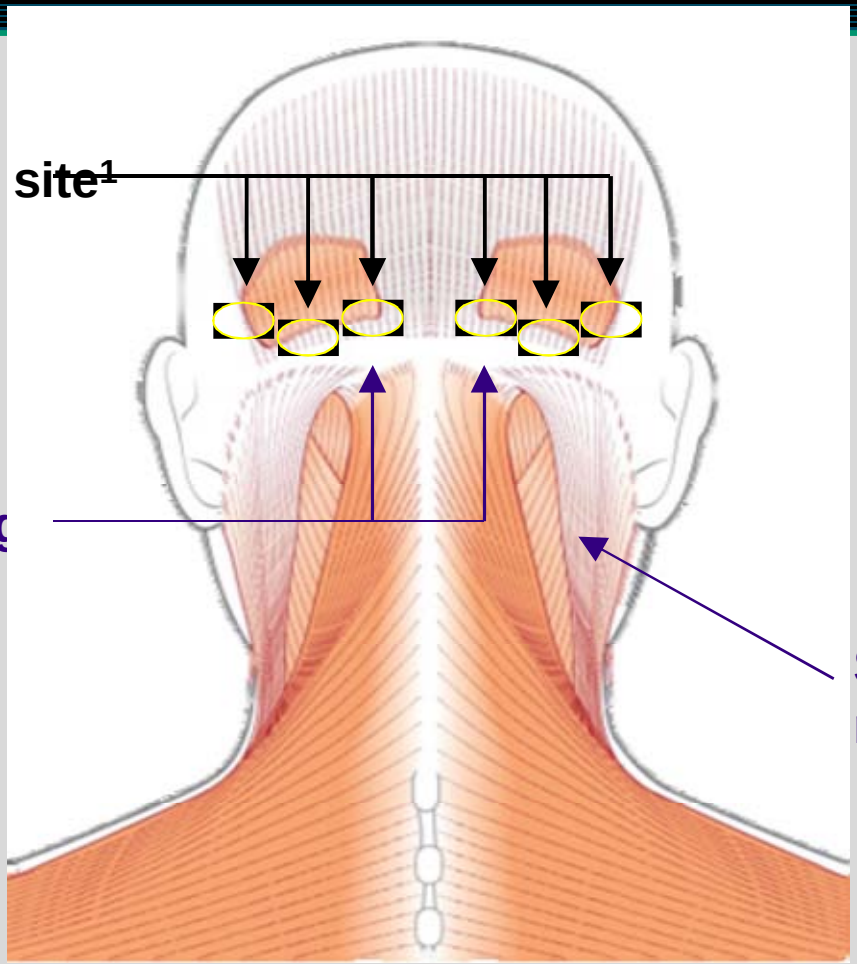
**Patient position:** Supine[1]

**Dose:** 4 injections of 0.1 mL on each side (a total of 40 U divided into 8 sites)[1]

**1.** Blumenfeld AM *et al. Headache* 2010;**50**:1406–18.

# *Injection Site: Occipitalis*

**Occipitalis: 5 U at each site**[1]

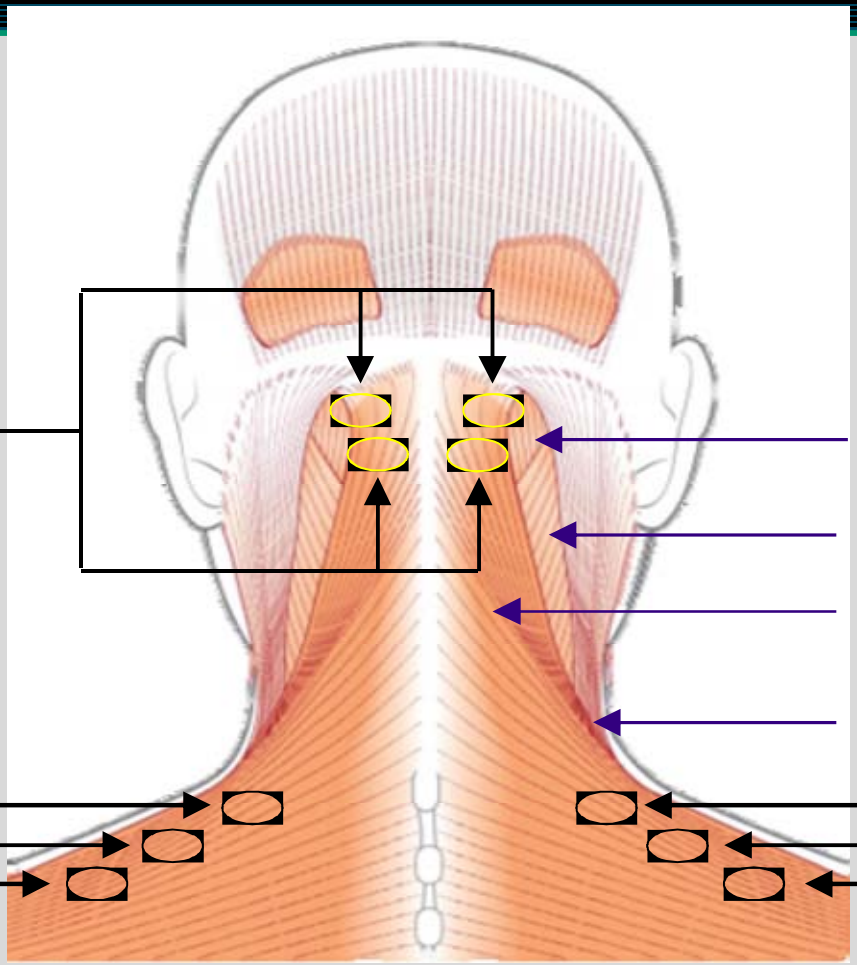



**Patient position:** Sitting[1]

**Dose:** 3 injections of 0.1 mL on each side (a total of 30 U divided into 6 sites)[1]

**1.** Blumenfeld AM *et al. Headache* 2010;**50**:1406–18.

# *Injection Sites: Cervical Paraspinals and Trapezius*

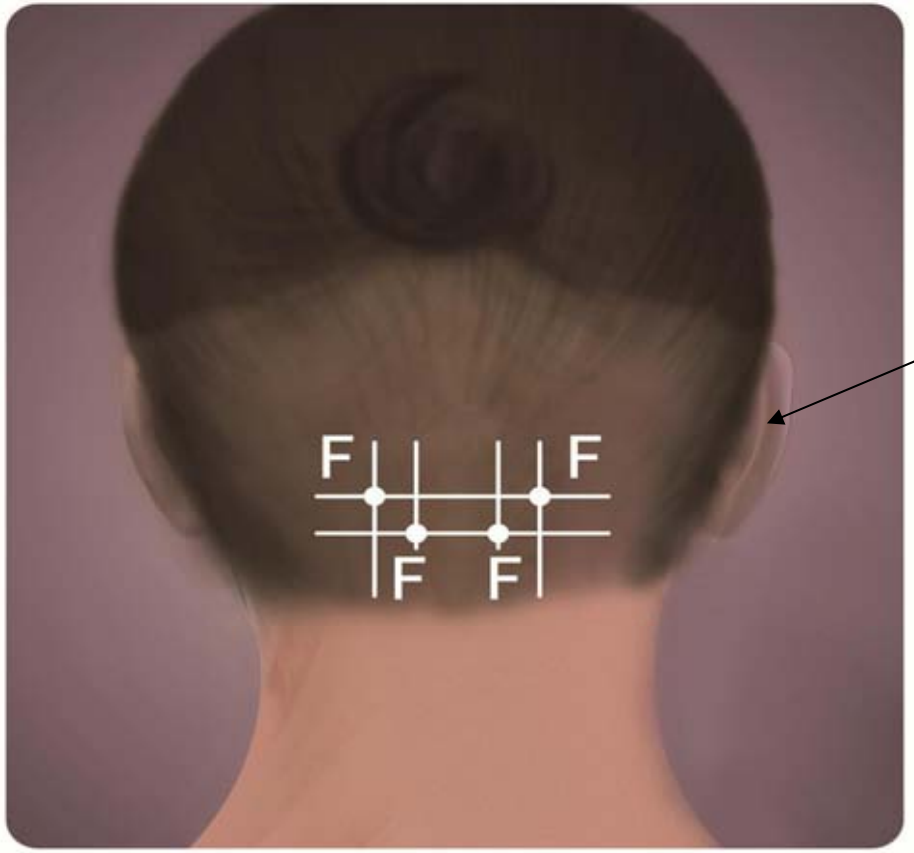



**Patient position:** Sitting[1]

**Dose:** 5 injections of 0.1 mL on each side (a total of 50 U divided into 10 sites)[1]

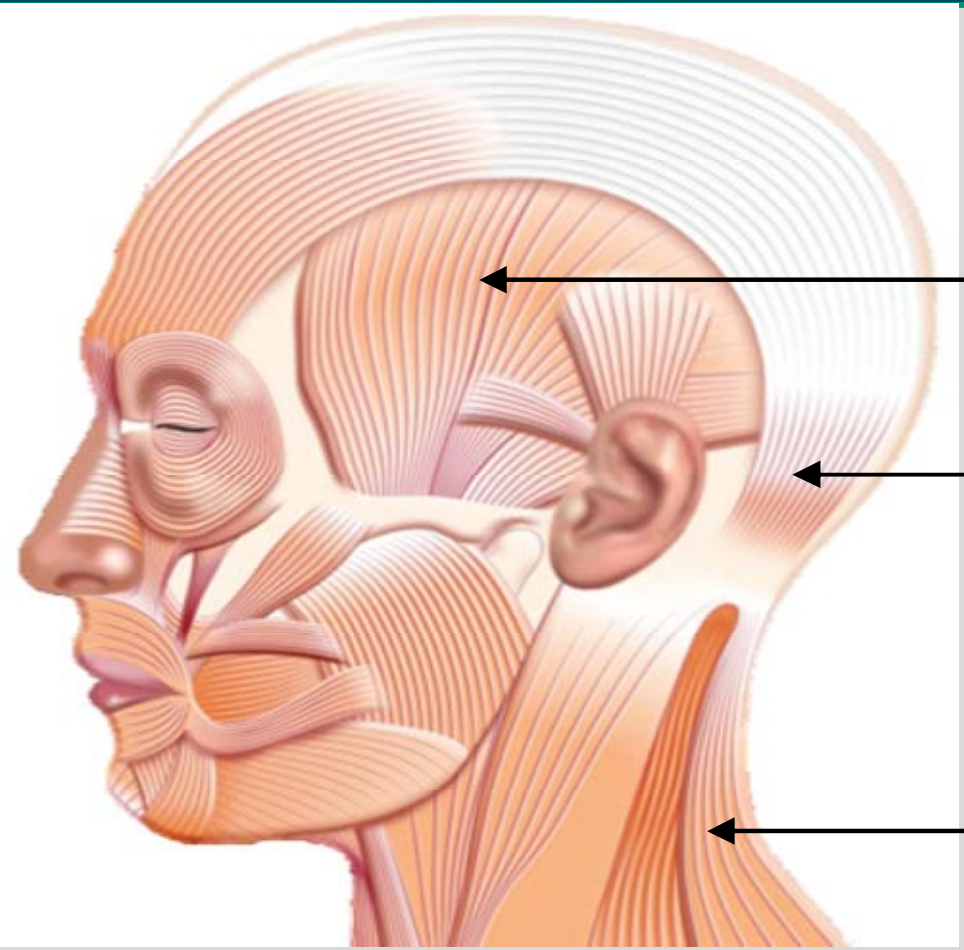
1. Blumenfeld AM *et al. Headache* 2010;**50**:1406–18.

# *Simplified Instructions: Cervical Paraspinals*




**Hairline shaded in diagram**

# *Injection Sites: The Follow-the-Pain Paradigm*



**Temporalis** (2 X 5 U). Up to an additional two doses in the right or left temporalis muscle or both, at the points of greatest pain[1]

**Occipitalis** (2 X 5 U). Up to an additional two doses in the right or left occipitalis muscle or both, at the points of greatest pain[1]

**Trapezius** (4 X 5 U). Up to an additional four doses in the right or left trapezius muscle or both, at the points of greatest pain[1]

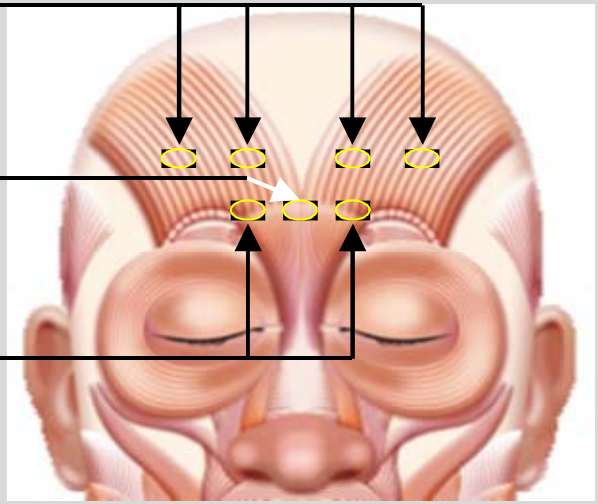
**1.** Blumenfeld AM *et al. Headache* 2010;**50**:1406–18.

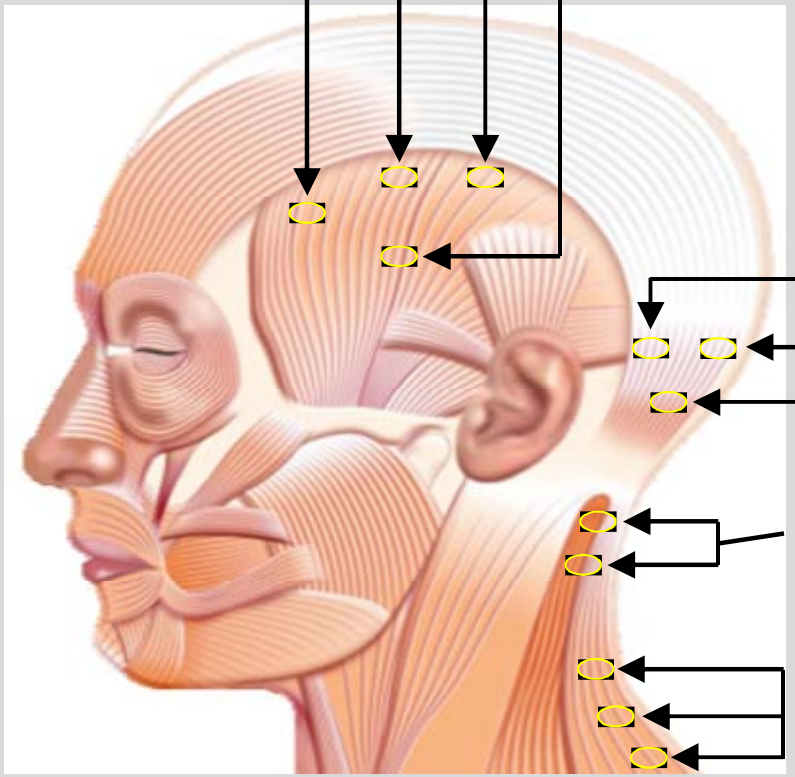
# *Summary PREEMPT Paradigm Injection Sites*

**Frontalis:**
**4 x 5 U[1]**

**Procerus:**
**1 x 5 U[1]**

**Corrugator:**
**2 x 5 U[1]**





**Temporalis:**
**8 x 5 U[1]**

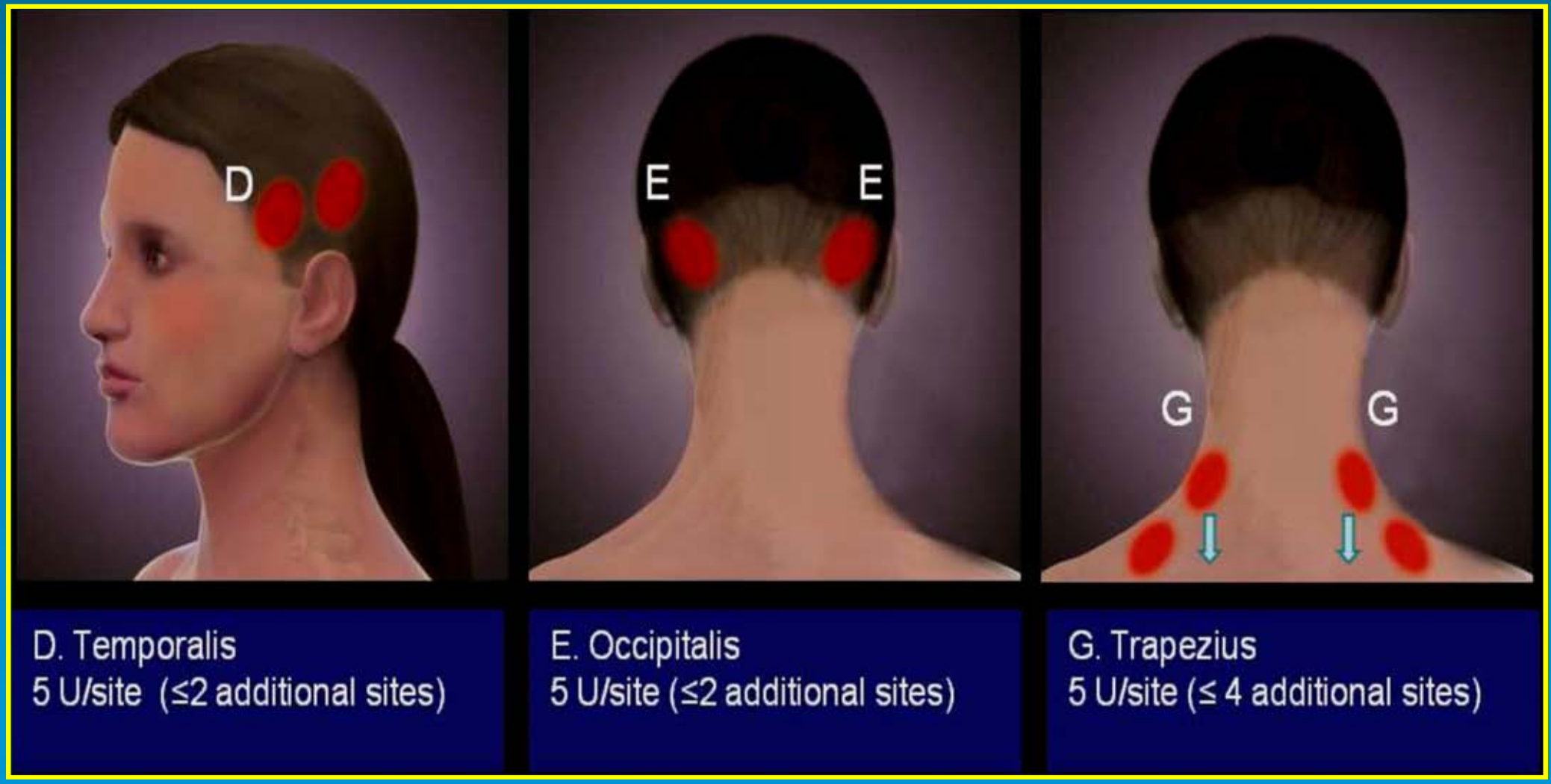
**Occipitalis:**
**6 x 5 U[1]**

**Cervical paraspinals:**
**4 x 5 U[1]**

**Trapezius:**
**6 x 5 U[1]**

1. Blumenfeld AM *et al. Headache* 2010;**50**:1406–18.

# *Follow-The-Pain-Strategy*



# *PREEMPT Summary: OnabotulinumtoxinA Efficacious and Well Tolerated in Chronic Migraine*

- Early treatment superior to delayed treatment
- Significant improvement in multiple headache symptoms
  - Frequency of headache days and episodes
  - Frequency of migraine days and episodes
  - Frequency of moderate/severe headache days
  - Cumulative number of headache hours on headache days
- Significant improvements in disability and functioning
  - Mean HIT-6 scores and proportion of patients with severe HIT-6 score
- Well tolerated; low discontinuation rates due to AEs
  - Serious AEs in 4.8% of BOTOX® patients and 2.3% of placebo patients



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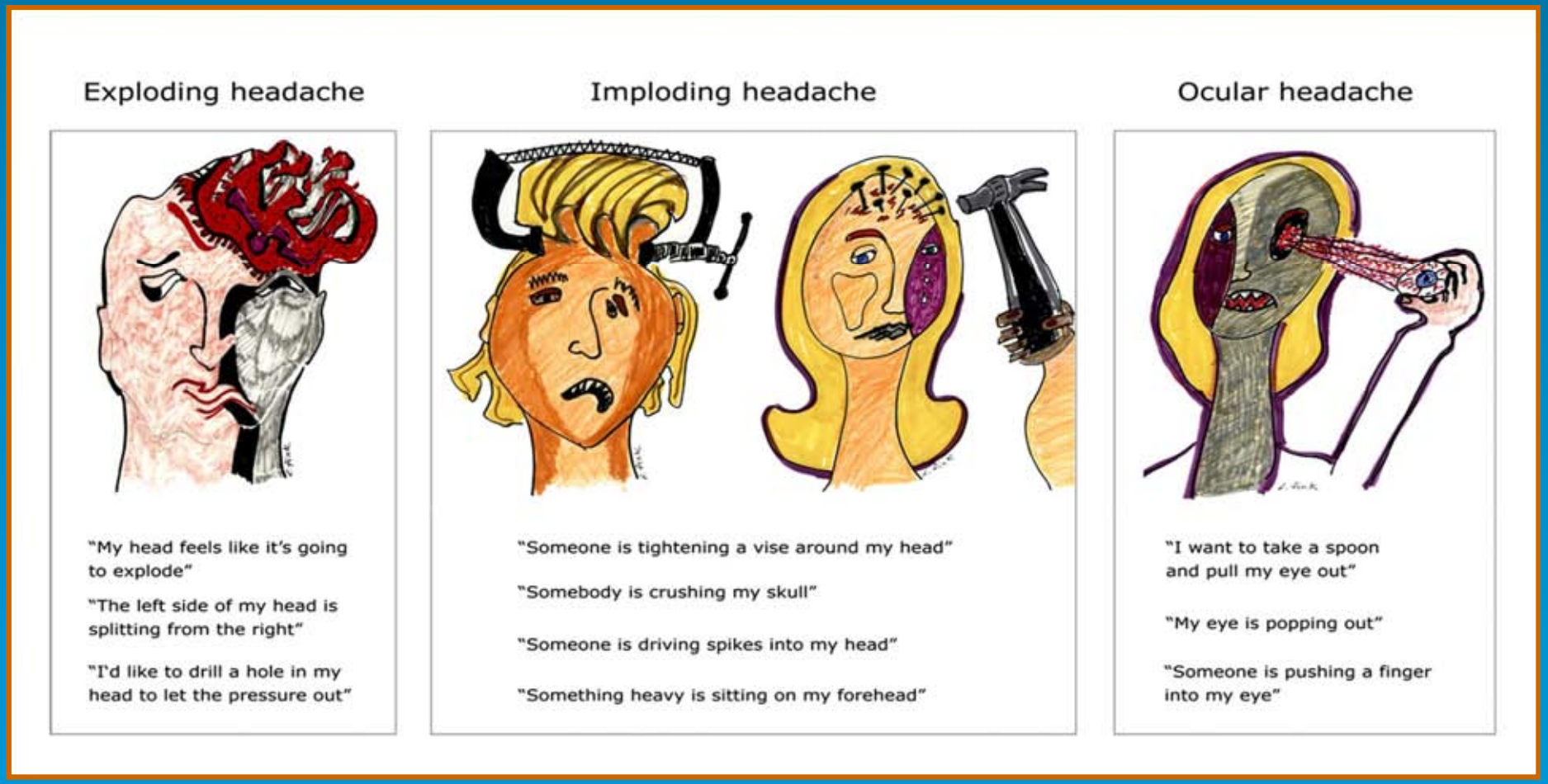
# *Minimizing Adverse Events*

- Lid ptosis –
  - Inject lying down
  - Angle away from the eye
- Brow ptosis
  - Some may be inevitable for certain individuals
  - Avoid lateral brow ptosis (current technique avoids)
- "Hourglass" head shape (temporalis atrophy)
  - Avoid high doses in anterior temporalis
- Neck weakness and pain
  - Avoid deep paraspinal injections
  - Avoid injections through the trapezius into medial paraspinal muscles especially in thin-necked individuals

# *Predictors of Response to Botulinum Neurotoxin*

Not aura, photo, phono, or osmophobia, nausea, vomiting, neck tenderness, or allodynia




Burstein R, PAIN 2007

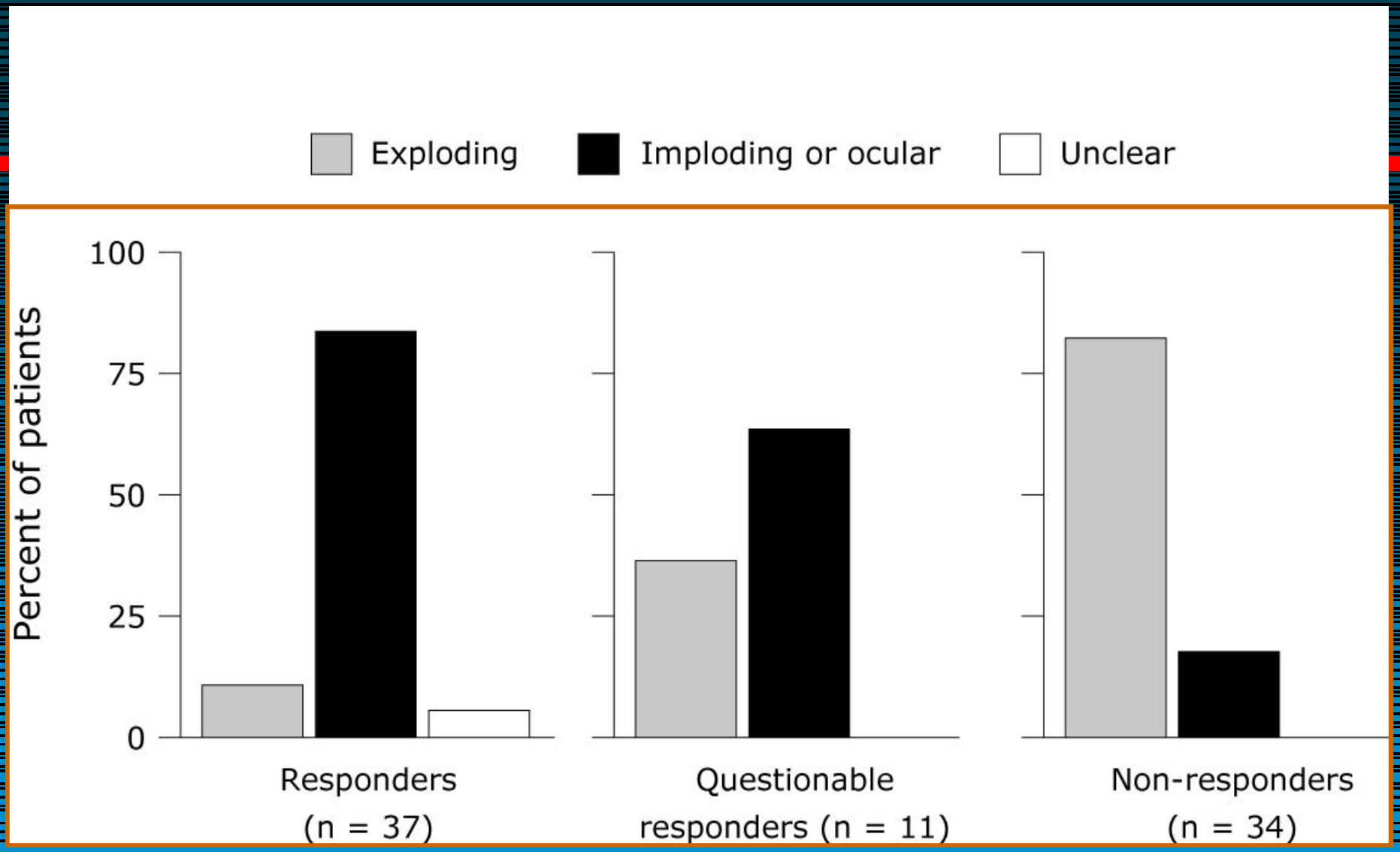
# *Possible Predictors of Response to BTX-A in CM*

| Headache Description | N* | Responders† | Nonresponders‡ |
|---|---|---|---|
| Exploding | 27 | 5 (19%) | 21 (81%) |
| Imploding | 31 | 29 (94%) | 2 (6%) |
| Ocular | 5 | 5 (100%) | 0 |

* Pooled data from prospective (n = 27) and retrospective (n = 36) open-label studies.
† ?≥30% reduction in number of migraine days per month (attack frequency x attack duration) vs. baseline.
‡ No change or ?•33% reduction in number of migraine days per month vs. baseline.



Jakubowski M et al. *Pain*. 2006;125:286-295.






Burstein, Dodick, Silberstein; American Academy of Neurology, 2006

# *Randomized, D-B, P-C, Cross-over Study*

- 8 months duration (2 x 4 months)
- Botulinum toxin type A (80 U)
- Quantitative sensory testing for CA
- *Primary efficacy parameters*
  - Migraine frequency, total number of days with headache, pain global assesment
- *Secondary efficacy parameters*

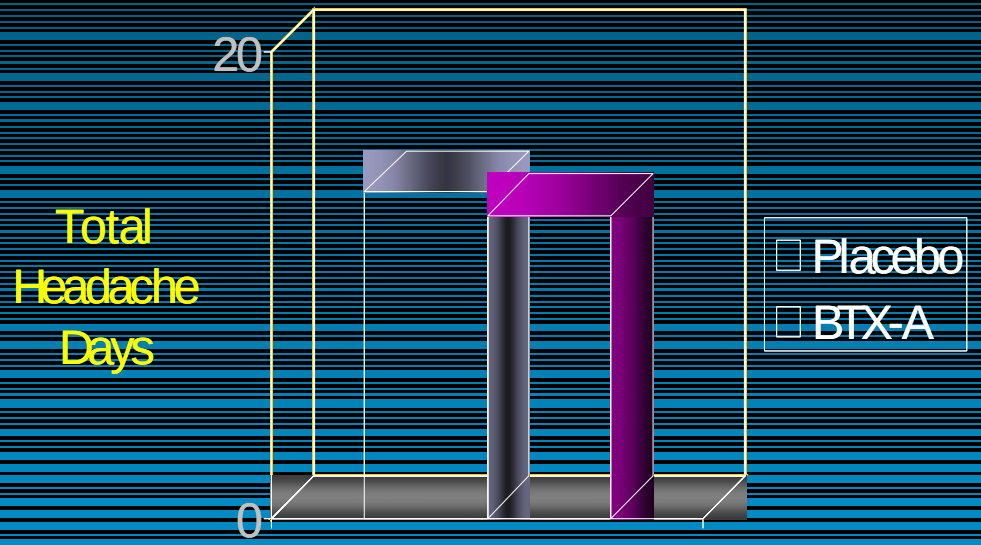
  Reduction of acute anti-migraine drugs



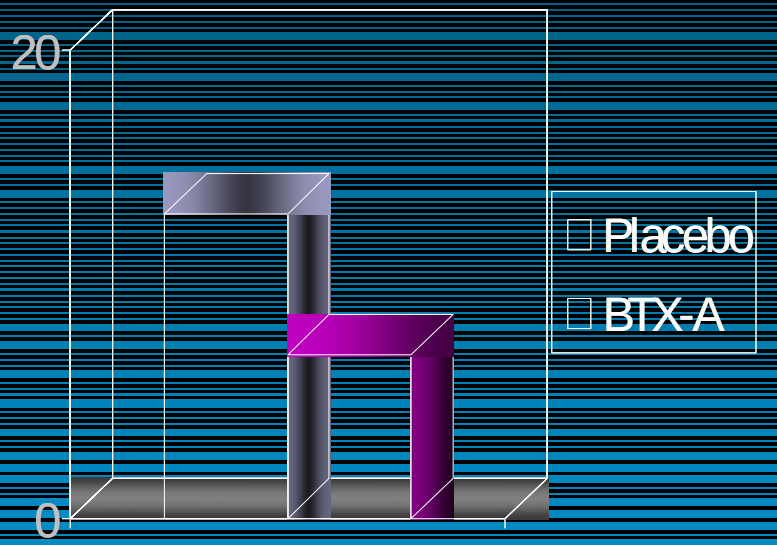
***Relja and Mileti?¸Cutaneous Allodynia in Migraine Patients as Predictive Factor for Effectiveness of Botulinum Toxin Treatment. AAN 2007***

# *Headache Days in Patients*

## Without CA



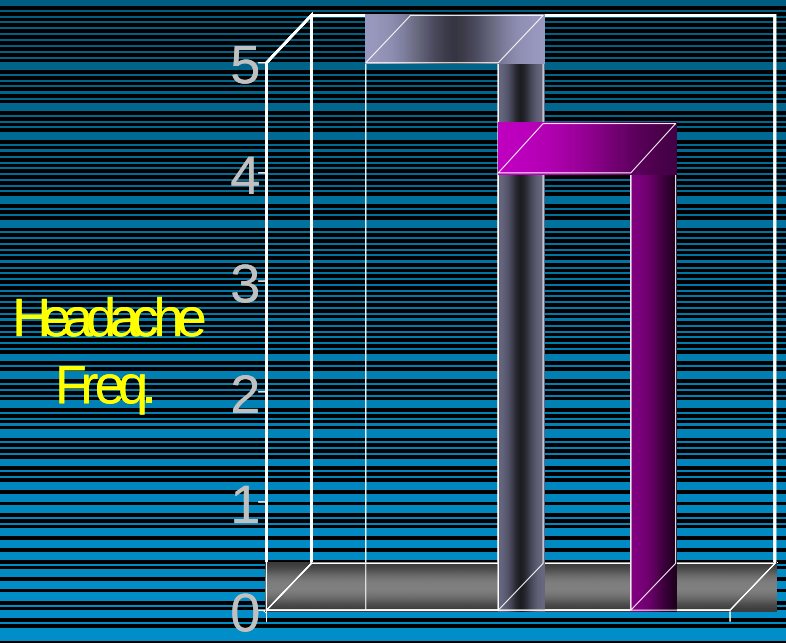

## With CA



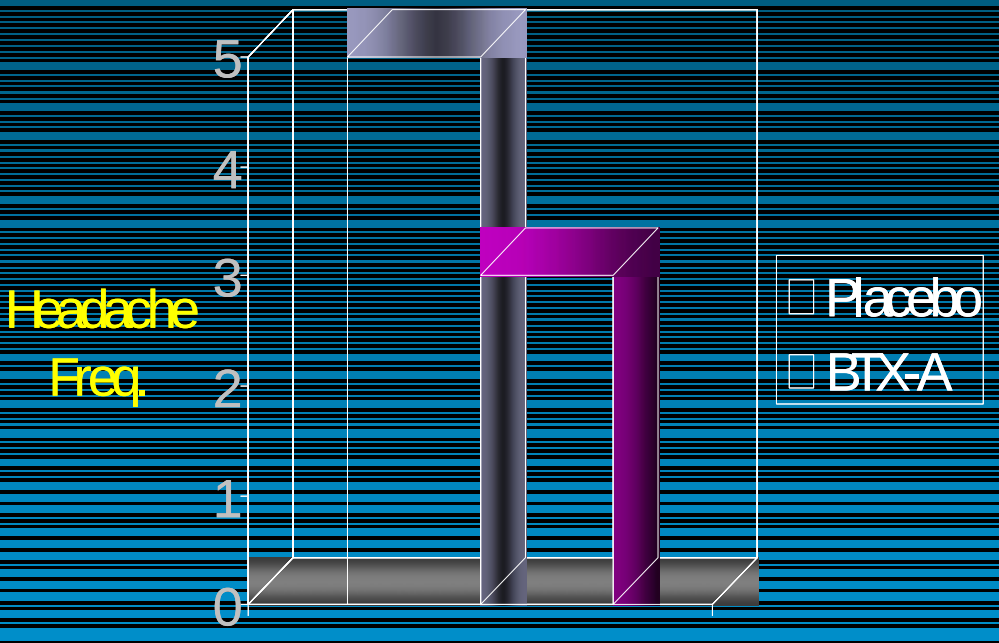

Relja and Mileti?: AAN 2007

# *Headache Frequency in Patients*

## Without CA




## With CA




Relja and Mileti?;,AAN 2007

# *Patients with CA: Conclusion*

- Significant reduction in migraine frequency and headache days with BTX-A treatment compared to placebo
  - Acute anti-migraine drugs significantly reduced
- CA could be a predictive factor for response to BTX-A therapy in migraine
- Long-term follow-up study needed

**Relja and Mileti?ÂAAN 2007**

# *OnabotulinumtoxinA Conclusions*

- Effective, safe, and well-tolerated treatment for CM and MOH headache prophylaxis in adults
- Significant improvement in multiple headache symptoms
  - Frequency of headache days and episodes
  - Frequency of migraine days and episodes
  - Frequency of moderate/severe headache days
  - Cumulative number of headache hours on headache days
- Significant improvements in disability and functioning,
  - Mean HIT-6 scores and proportion of patients with severe HIT-6 score



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# *BTX in Headache Disorders*

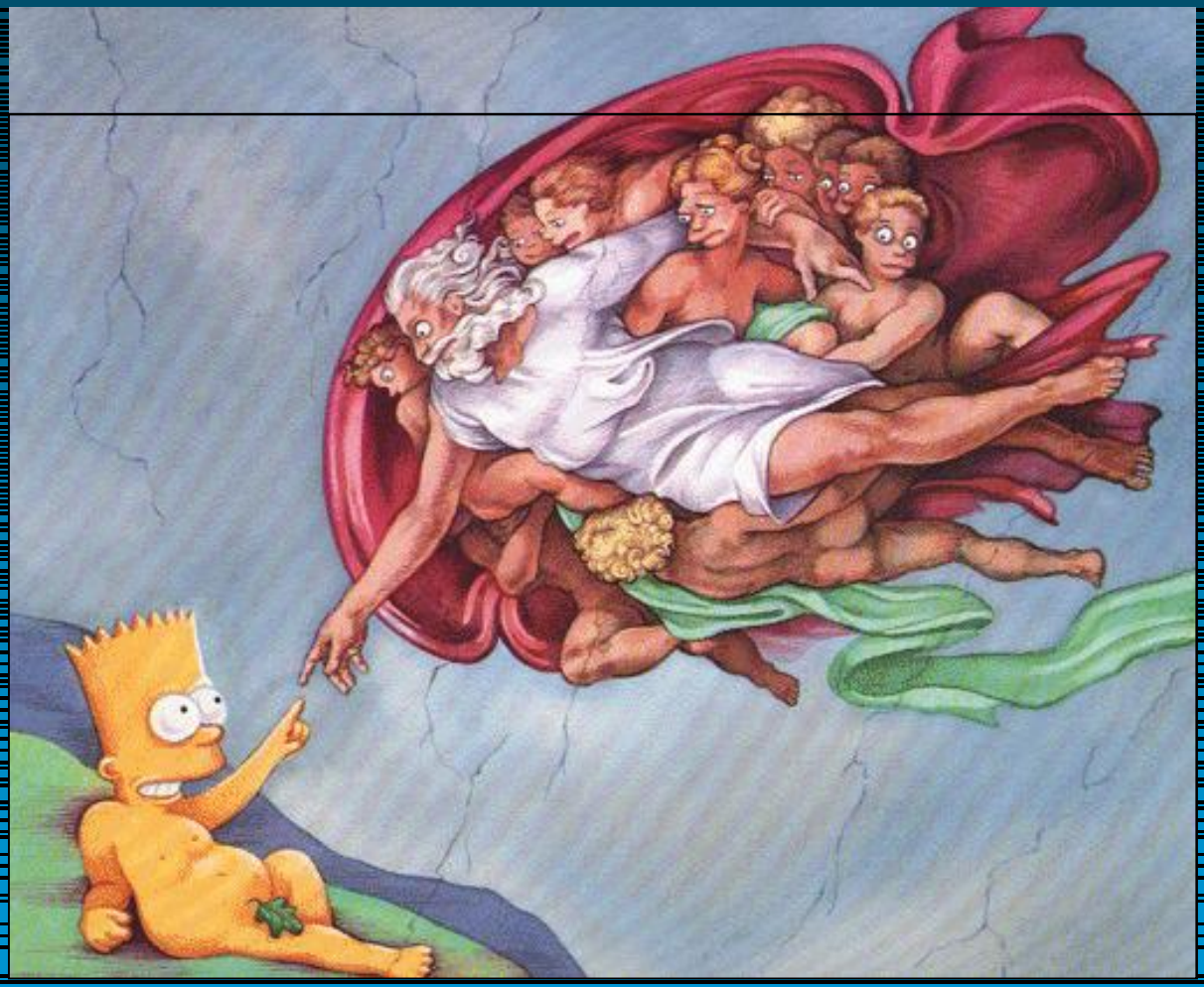
## Where does BTX work in headache?

- Chronic migraine, and MOH
  - Especially Imploding or ocular headache?
  - Allodynia?

## Where might BTX work in headache?

- Frequent episodic migraine
- Trigeminal neuralgia

# *Treating Headache can be Divine*



"Pain is a more terrible lord of mankind than even death itself."

-Albert Schweitzer