

Headache and Facial Pain

Annual Neurotoxin Webinar

Cleveland Clinic

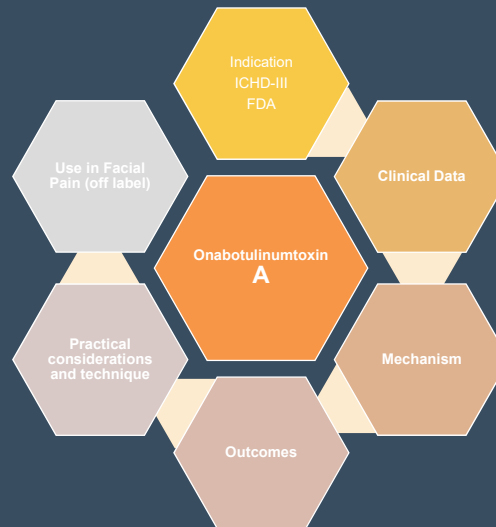
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Neurological Institute
Cleveland, OH



Objectives

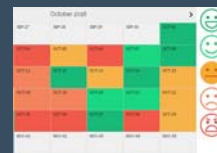
- Describe criteria for chronic migraine
- Review benefits of onabotulinumtoxinA beyond headache frequency reduction
- Discuss data for onabotulinumtoxinA in other facial pain disorders

Outline



Case

A 37-year-old woman presents with a **severe** headache which she describes as a **pressure** sensation lasting for eight hours. The headaches usually occur on the right side of her head. They are **not** associated with photophobia or phonophobia. She reports **nausea**. The headache **worsens with activity**. What is the most likely diagnosis?



15 HA days



What is the most likely Diagnosis?

A 37-year-old woman presents with a **severe** headache which she describes as a **pressure** sensation lasting for eight hours. The headaches usually are right sided. They are **not** associated with photophobia or phonophobia. She reports **nausea**. The headache **worsens with activity**.

She is using Excedrin or triptan every other day. She has 15 headaches per month.

- A. Chronic migraine
- B. Chronic tension type headache
- C. Chronic migraine and medication overuse headache
- D. Chronic tension type headache and medication overuse headache

ICHD-III Criteria for Migraine

1.1 Migraine without Aura

At least 5 headaches
Headaches lasting 4-72 Hours

At least **two** of the following **four**

Pulsating ✓

Unilateral ✓

Moderate – Severe ✓

Activity (worsening) ✓

At **least one** of the following:

1. Nausea ✓

2. Photophobia **and** phonophobia

1.3 Chronic Migraine

At least 15 Headache days/mo, 3 months
At least 8 days with migraine features

- Meet criteria for Migraine WO aura
- Meet criteria for Migraine W aura

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**Patients with medication overuse should be diagnosed with both MOH and CM*

What is the FDA approved definition of Chronic Migraine?

- Headache at least 15 days/mo, of which 8 meet criteria for migraine
- Headache at least 15 days/mo, at least 4 hours per day, at least 15 days meet migraine criteria
- Headaches at least 15 days per month, 4 hours per day, of which 8 headaches respond to migraine treatment
- Headaches occurring at least 15 days/mo, with headaches lasting 4 hours per day or longer

Differences between ICHD III and FDA

ICHD – III Criteria

1.3 Chronic Migraine

At least 15 Headache days/mo, 3 months

At least **8 days** with migraine features

- Meet criteria for Migraine WO aura
- Meet criteria for Migraine W aura

Excludes tension type headache

Excludes secondary headache

Excludes sudden onset headache

Must have migraine features

FDA Definition

Chronic Migraine

At least 15 Headache days/mo lasting at least 4 hours

No mention of Secondary or Primary

No mention of onset

No mention of duration

No mention of severity

ICHD III criteria
OnabotulinumToxinA US prescribing information, 2010:
[Http://www.allergan.com/assets/pdf/botox_pi.pdf](http://www.allergan.com/assets/pdf/botox_pi.pdf)

Differences between ICHD III and FDA

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Why is Chronic Migraine Important?



Only 36% of patients received a Chronic Migraine diagnosis despite meeting the criteria^{3,4}

1. CDC WONDER website. Accessed 2015
2. Natoli et al. *Cephalalgia* 2010
3. Lipton et al. *Cephalalgia*. 2015
4. Data on file, Allergan, Inc.; 2014 Barriers to Chronic Migraine Care.

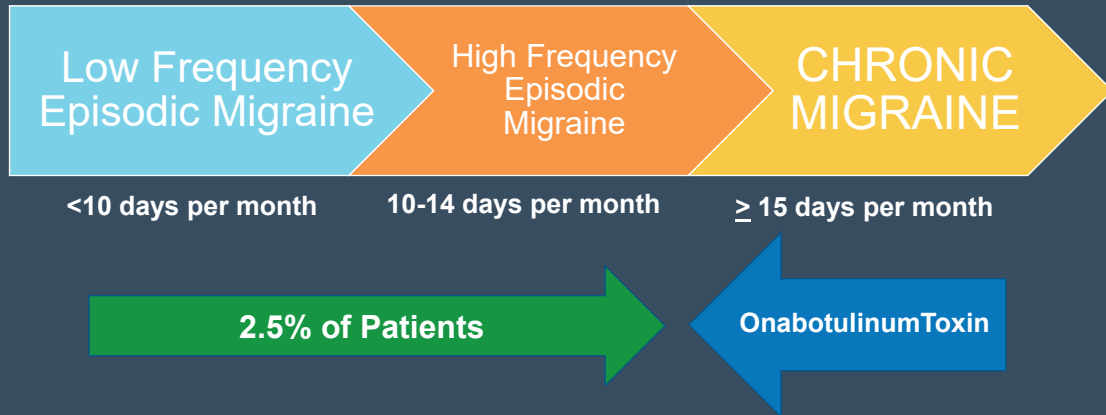
Why is Chronic Migraine Important?

- Significant Disability
- Associated with twice as much anxiety and depression
- 2x as likely to visit PCP
- 3x as likely to see neurology
- 3x as likely to be admitted



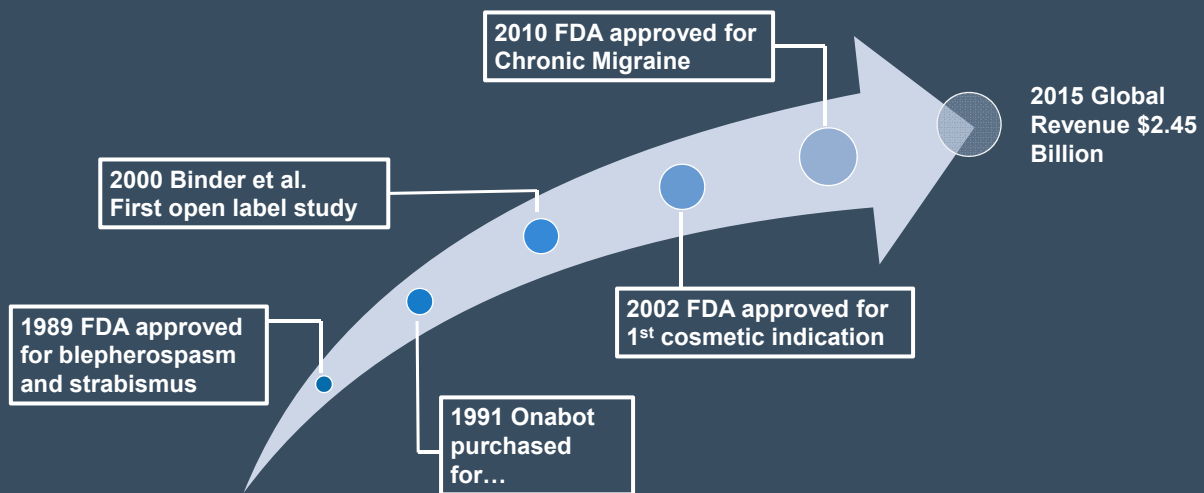
1. Blumenfeld et al. *IBMS. Cephalalgia* 2010

Progression of Migraine



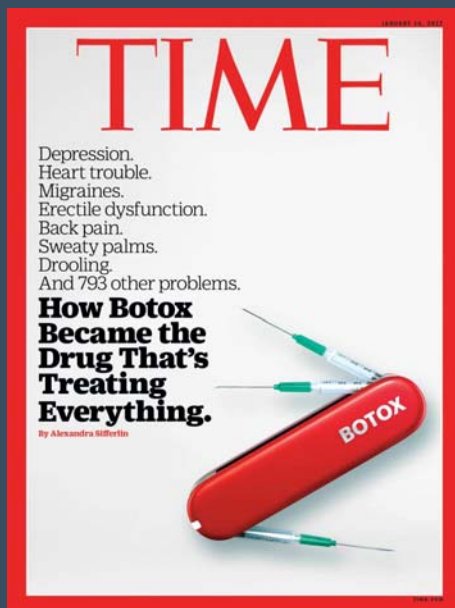
Lipton and Bigal. Headache 2006

Onabotulinum Timeline



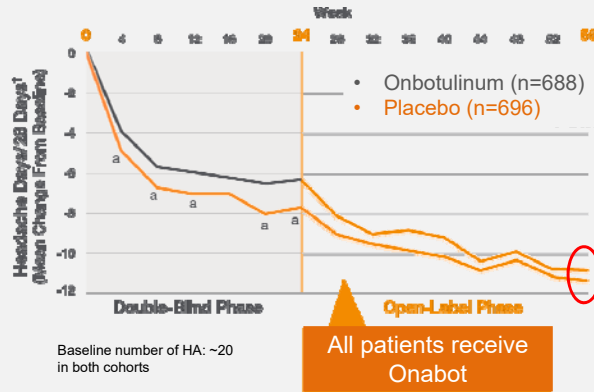
Approximately, how many patents are held for current and potential Onabot applications?

- A. 50
- B. 200
- C. 500
- D. 800



Mean change from Baseline Pooled Analysis Preempt 1,2

- Patients on onabotulinum
- 8-9 fewer headache days
 - 75% with >50% reduction in headache frequency
- Placebo group does not catch up to Onabot cohort



1. Data on file, Allergan, Inc.; PREEMPT 1 Final Report.
2. Data on file, Allergan, Inc.; PREEMPT 2 Final Report.

PREEMPT Endpoints

Parameter	European Union Trial	United States Trial
Migraine days		
Headache days		
Headache free days		
Triptan use		
All acute medication use		
Medication overuse		
50% responder rate		
Disability measure		

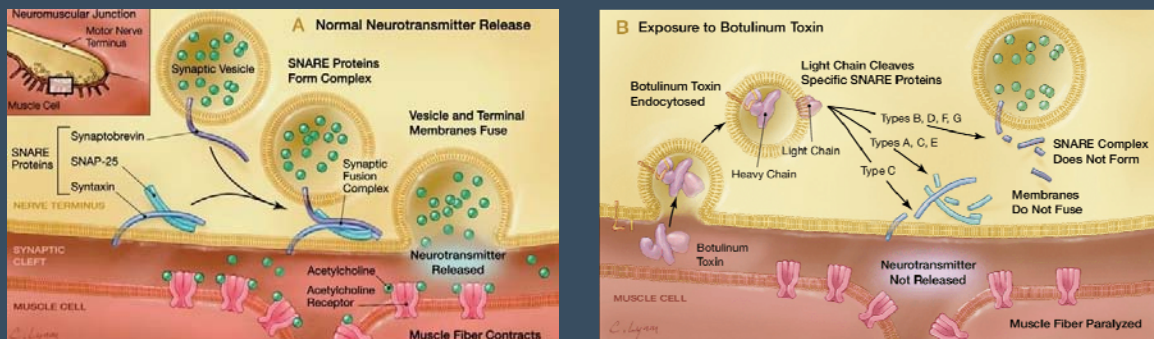
Dodick et al. Headache 2010

PREEMPT Onabot Side Effects

	Onabot (n=687)	Placebo (n=692)
Total Treatment Related AE %	29.4	12.7
Neck Pain	6.7	2.2
Muscular weakness	5.5	0.3
Eyelid Ptosis	3.2	0.3
Musculoskeletal pain	2.2	0.7
Injections site pain	3.2	2.0
Headache	2.9	1.6
Myalgia	2.6	0.3
Musculoskeletal stiffness	2.3	0.7

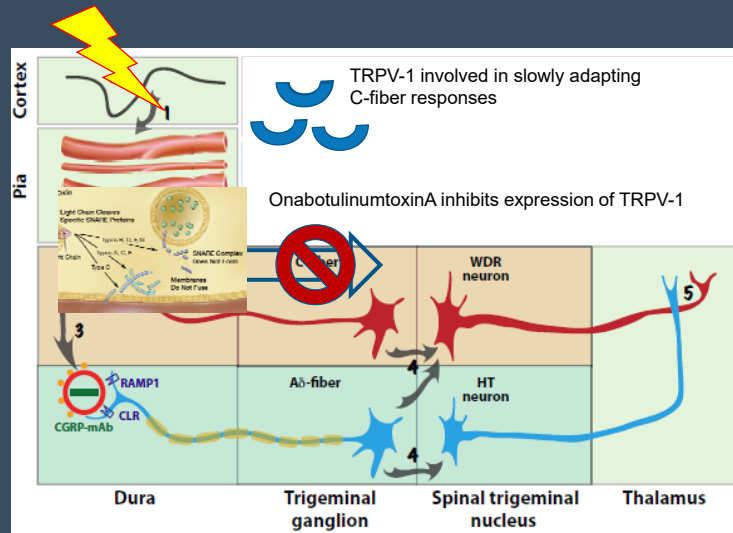
Dodick et al. Headache 2010

Onabotulinum Mechanism of Action



Blumenfeld. Onabotulinum for Dentistry. 2015

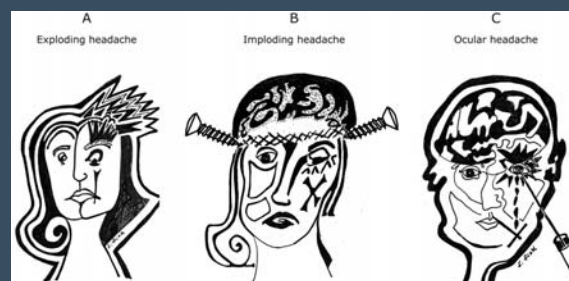
Onabotulinum Mechanism of Action



Melo-Carrillo A, et al. *J. Neurosci.* 2017; 37:10587–10596.
 Hyun-Mi OH and Myung Eun Chung. *Toxins* 2015 3:127–3154
 Zhang et al. *Cephalalgia* 2016 36(9) 875–886

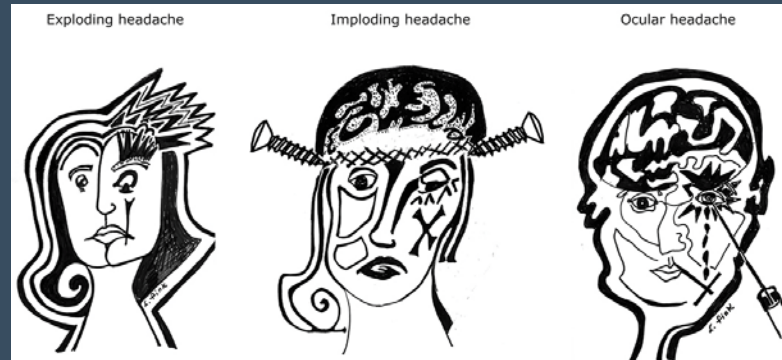
Does Onabotulinum work preferentially on certain types of pain?

- A. Exploding headache
- B. Imploding headache
- C. Ocular Headache
- D. Works best in imploding and ocular headache



Does Onabotulinum work preferentially on certain types of pain?

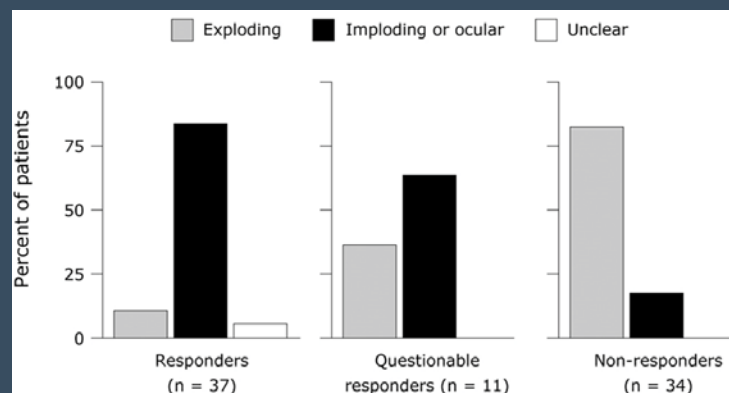
- 82 migraine patients
- Response to Onabot
 - Responders
 - Questionable
 - Non-responders
- Determine if response correlate with the type of pain



Burstein et al. Toxico 2009

Does Onabotulinum work preferentially on certain types of pain?

- 82 migraine patients
- Response to botox
 - Responders
 - Questionable
 - Non-responders
- Determine if response correlate with the type of pain



Burstein et al. Toxico 2009

Which of the following improve in patients treated with Onabotulinum?

- A. Headache Disability
- B. Depression
- C. Anxiety
- D. All of the Above

Patient Reported Outcomes

- HIT 6
36-78
 - ≤49 No impact
 - 50-55 Moderate impact
 - 56-59 Substantial Impact
 - ≥60 Severe impact

When you have headaches, how often is the pain severe?

never rarely sometimes very often always

How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

never rarely sometimes very often always

When you have a headache, how often do you wish you could lie down?

never rarely sometimes very often always

In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

never rarely sometimes very often always

In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

never rarely sometimes very often always

In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

never rarely sometimes very often always

+ + + +
 COLUMN 1 COLUMN 2 COLUMN 3 COLUMN 4 COLUMN 5
 6 points each 8 points each 10 points each 11 points each 13 points each

Patient Reported Outcomes

MIDAS

- 0-5 Little or no disability
- 6-10 Mild disability
- 11-20 Moderate disability
- ≥ 21 Severe disability

Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months. Please take the completed form to your healthcare professional.

- _____ 1. On how many days in the last 3 months did you miss work or school because of your headaches?
- _____ 2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)
- _____ 3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?
- _____ 4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)
- _____ 5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

PHQ 9

- 0-4 Minimal depression
- 5-9 Mild depression
- 10-14 Moderate
- 15-19 Moderate-Severe
- 20-27 Severe

The Patient Health Questionnaire (PHQ-9)

Patient Name _____ Date of Visit _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

GAD-7

- 1-4 Minimal anxiety
- 5-9 Mild
- 10-14 Moderate
- 15-21 Severe

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
<i>Add the score for each column</i>	+	+	+	+
Total Score (add your column scores) =				

>10, sensitivity and specificity greater than 80%

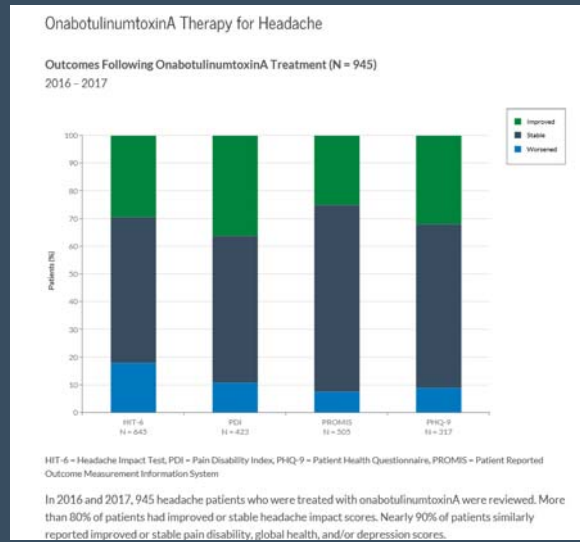
Jordan et al. PLOS One. 2017; 12(8)

Knowledge Program

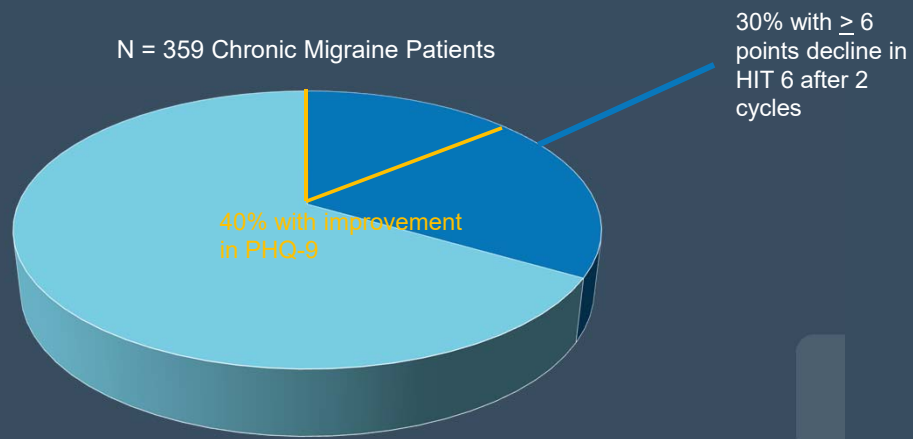
Patients seen in the Headache Clinic

- January 2008 – October 2015
- 161,690 visits
- 18,453 unique visits
- Mean HIT 6 score of 62.9

Outcomes following OnabotulinumToxin A 2016-2017



Does Onabot impact Depression?



COMPEL – Long term Onabot Outcomes

Blumenfeld et al. *The Journal of Headache and Pain* (2018) 19:13
DOI 10.1186/s10194-018-0840-8

The Journal of Headache
and Pain

RESEARCH ARTICLE

Open Access

Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study



Andrew M. Blumenfeld^{1*}, Richard J. Stark², Marshall C. Freeman³, Amelia Orejudos⁴ and Aubrey Manack Adams⁴

1. What is the effect on Quality of Life outcomes?
2. When does the benefit plateau?

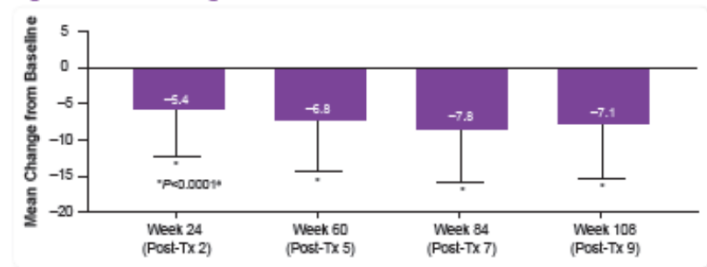
COMPEL – Long term Onabot Outcomes

HIT-6

Average HIT 6
64.7

By 108 weeks
57.6

Figure 2. Mean Change from Baseline in HIT-6 Scores

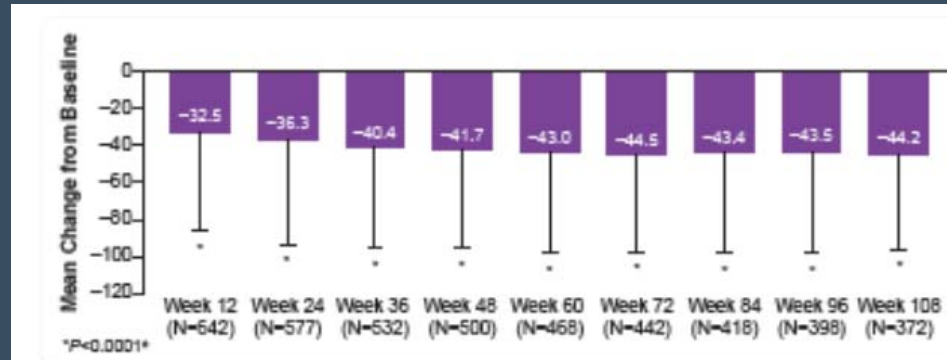


HIT-6=6-item headache impact test
NOTE: Missing data were imputed using modified last observation carried forward (mLOCF) method
* Two-sided P-value comparing post-baseline visit to baseline from the paired t-test; significance level is 0.025

MIDAS

Baseline
average **78**

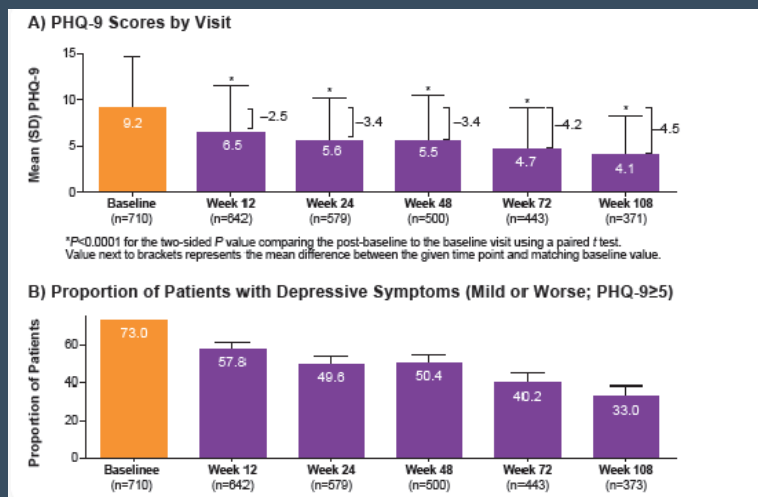
108 weeks,
reduction by
44.2 points



PHQ-9

Mean at baseline
9.2

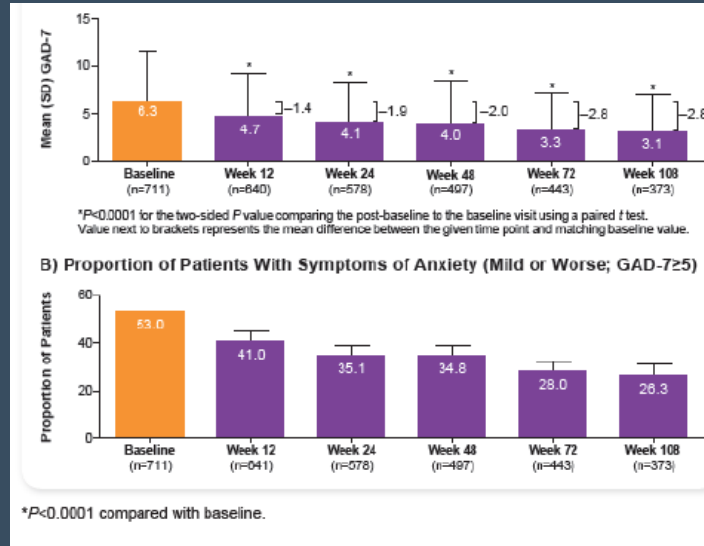
108 weeks,
reduction by
5 points, 4.1
(minimal depression)



GAD 7

Mean at baseline
6.3

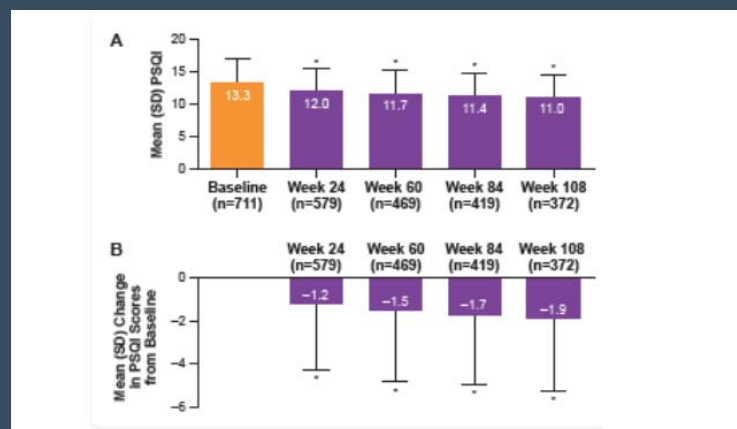
108 weeks,
reduction by
3.2 points, 3.1
(minimal anxiety)



Pittsburgh Sleep Quality Index

Mean at baseline
13.3

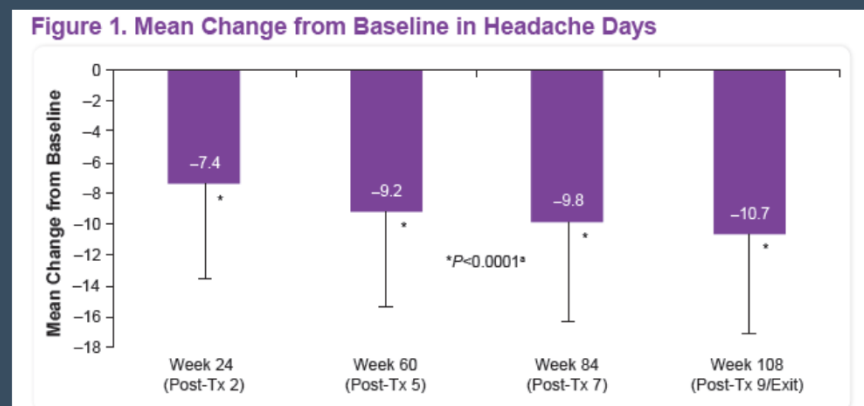
108 weeks,
reduction by
2 points, 11.0



How many cycles of Onabot are needed to establish efficacy?

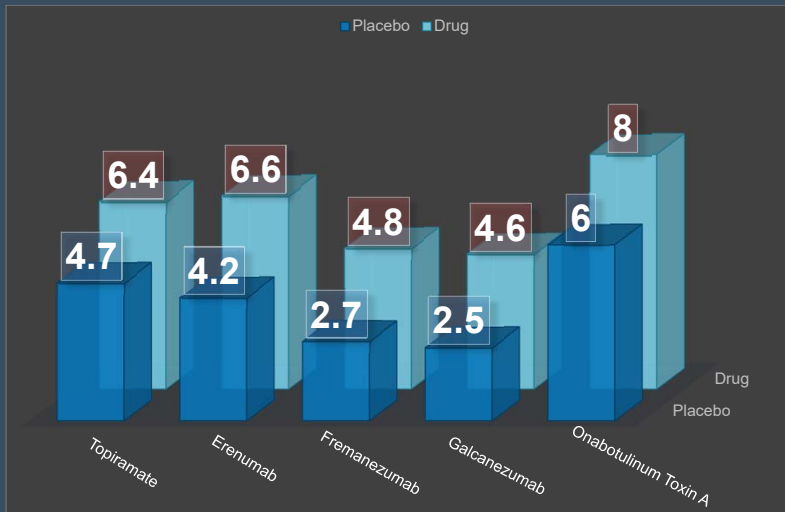
- A. 3 cycles, 9 months
- B. 9 cycles, 27 months
- C. 15 cycles, 45 months
- D. > 45 months

COMPEL Mean Change in HA days



Blumenfeld et al. Presented at the Diamond Headache Clinic Research and Educational Foundation Headache Update 2017

Chronic Migraine



Onabotulinum Toxin A

Preempt

- Onabotulinum 8
- Placebo 6

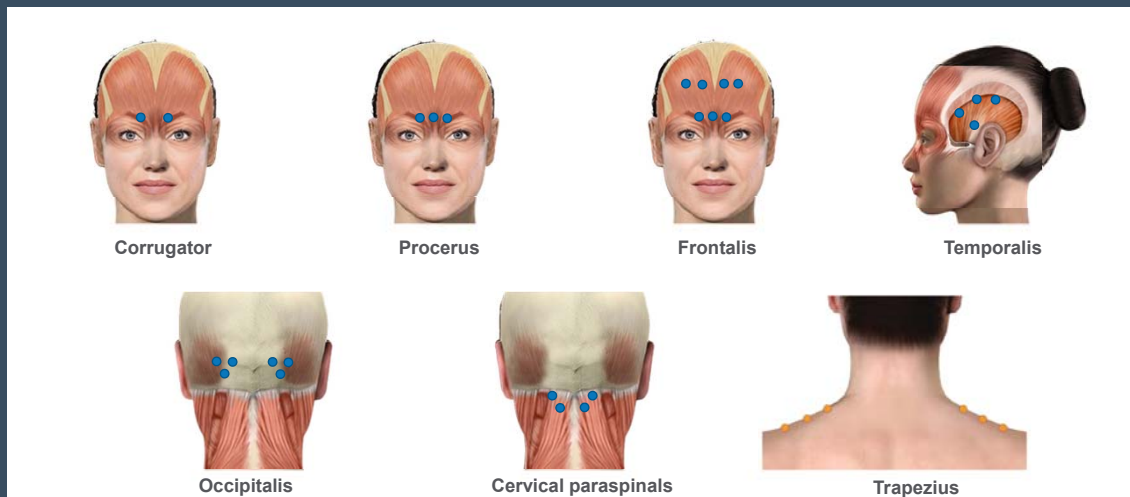
Compel

- Onabotulinum 10.7

Side effects, a different story

Deen et al. The Journal of Headache and Pain (2017) 18:96

Preempt Protocol

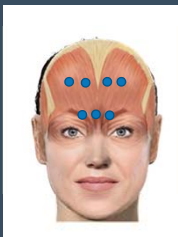


Corrugator



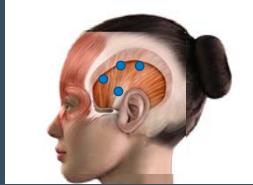
- Pulls eye brows down and medially
- Causes vertical wrinkles between the brows
- Too far superiorly results in **brow ptosis**
- Mild elevation of the medial eye brow is seen with corrugator weakness

Frontalis

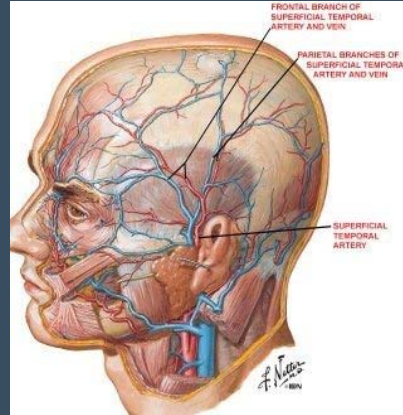


- Inject into upper third of the forehead, 2 fingerbreadths above the corrugator injections
- Lateral injections, one fingerbreadth from the medial injections
- Mid-pupillary line
- Weakness causes brow ptosis
- Lateral brow elevation occurs due to medial frontalis weakness

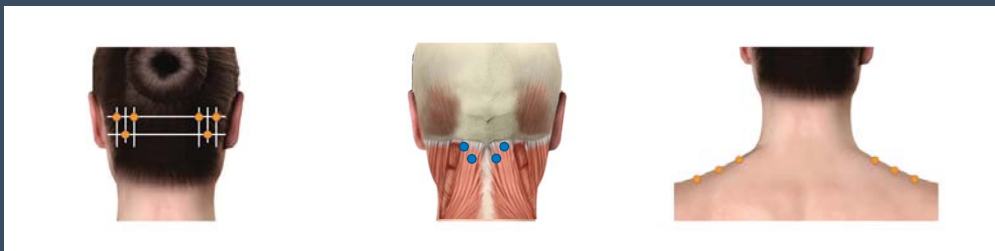
Temporalis



- Pulling back on the syringe
- Spread out injections if temporal hollowing

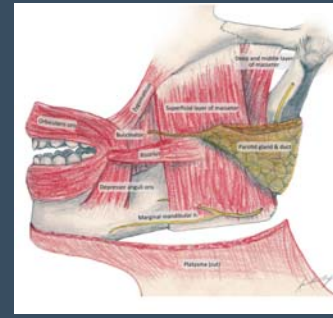
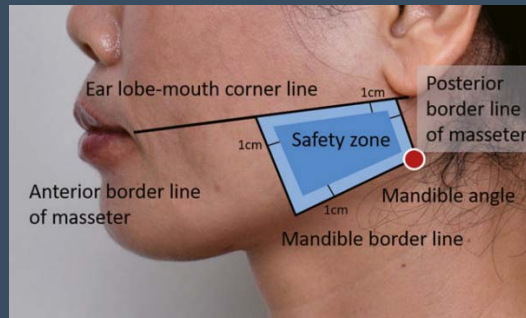
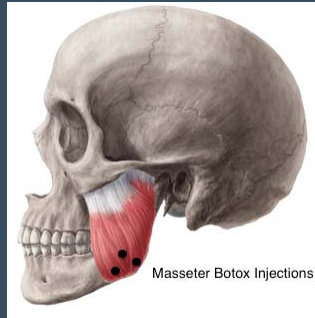


Cervical Paraspinals



- Keep injections within the hairline
- PREMPT – trapezius injections were associated with neck pain

Masseter Injections



HL Peng, JH Peng. Journal of Cosmetic Dermatology. 2017

Practical Considerations

- Recognize unique anatomy, no 2 patients are alike
- Focus on the muscle, not measurements, to adjust for individual anatomical variations
- Apply injection techniques that account for anatomical variability
- Consider injecting in the most superficial aspect of the muscle
- Consider depth and angle carefully
- Follow up patients who have side effects
- 155 Units → 200 Units (follow the pain) → decrease time between injections



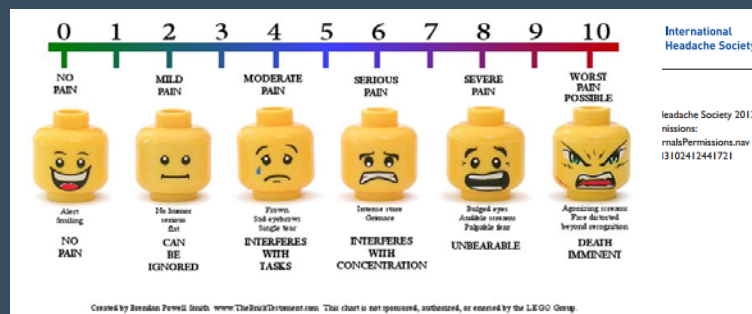
Onabotulinum for Trigeminal N

- Carbamazepine in 4 RCT demonstrated efficacy
- Only 50% of patients remain long term responders
- >600 mg/day can result in intolerable side effects
- Induction of liver enzymes

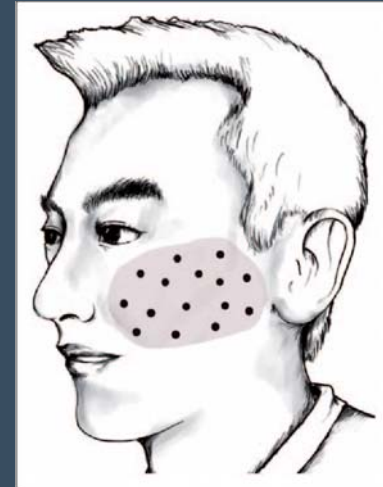
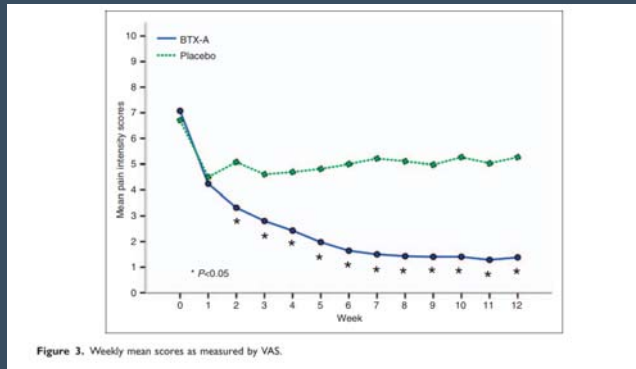
Burmeister et al. Trials 2015

Onabotulinum for Trigeminal N

- 42 patients randomized, onabotA vs saline
- > 50% reduction in pain (Visual Analogue Scale)
- 75 units total
- 15 sites (5u/site)
- Intradermal or submucosal

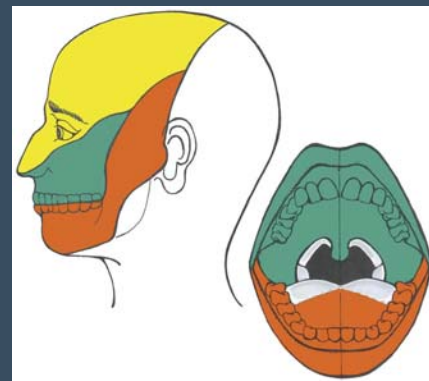
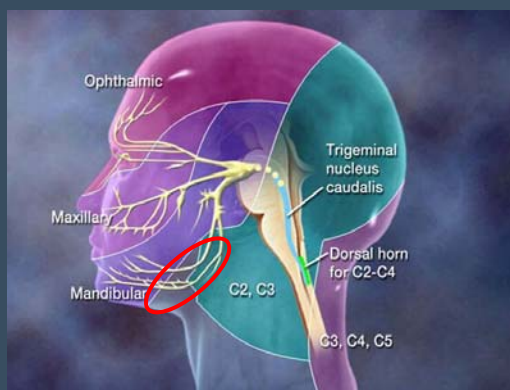


Onabotulinum for Trigeminal N



Wu et al. Cephalalgia 2012

Onabotulinum for Trigeminal Neuralgia



Summary of Onabotulinum Toxin in Trigeminal Neuralgia

- 4 Randomized Controlled Trials
- 178 Patients
- Doses range from 25 U to 75 U
- No standardized protocol
 - Trigger zones
 - Trigeminal nerve distribution

Summary

- Onabotulinumtoxin A is approved for Chronic Migraine
- Improvement is seen in headache frequency and PRO, over 2 years
- A minimum of 3 cycles to determine efficacy
- May be effective for Trigeminal Neuralgia