Botox treatment in CM prophylaxis from practice to rationale

박 미 영

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Edvard Munch, 절규 The Scream

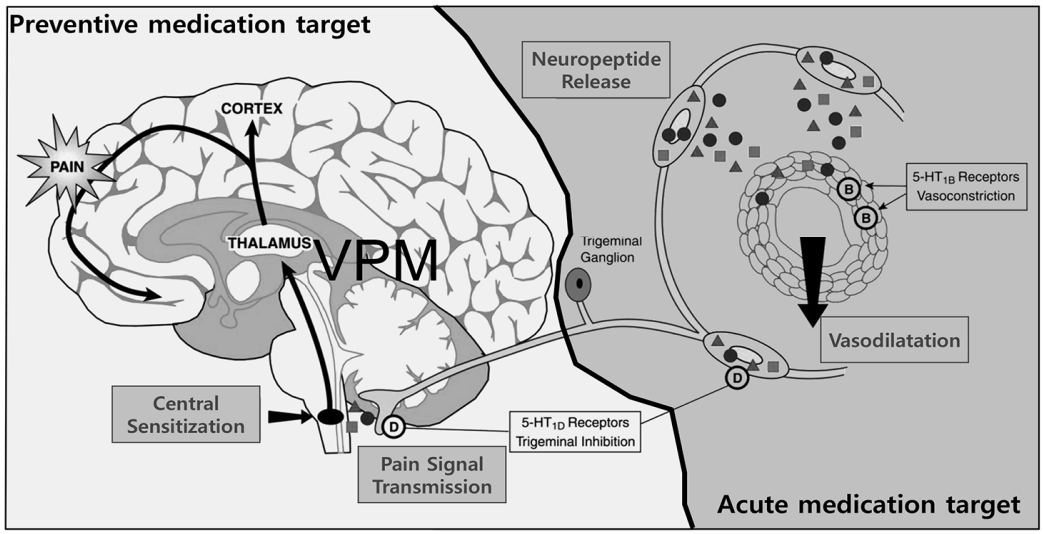
ICHD-3beta criteria for chronic migraine

A. Headache ≥15days for 3 ≥ Month
B. Patient had ≥attacks fulfilling ICHD -2 migraine without aura
C. On ≥8 day/month for >3months headache fulfills 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

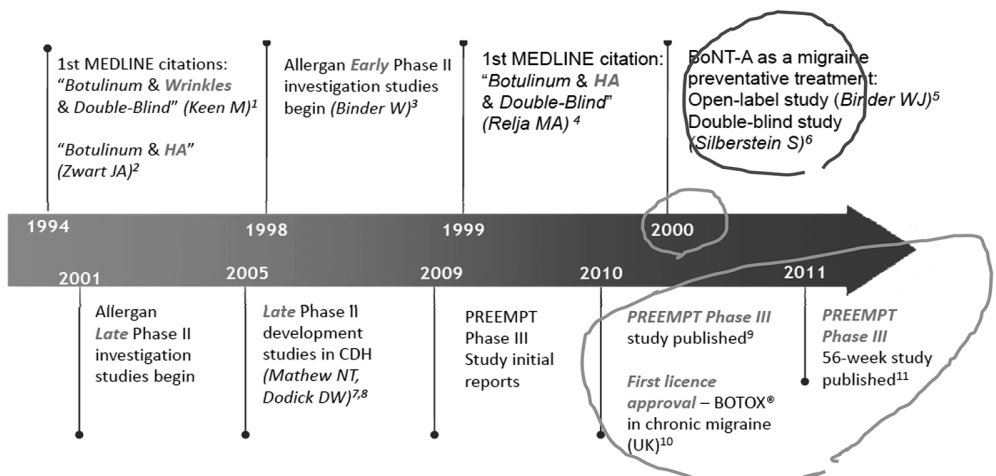
하루에 4시간 이상 지속되는 두통이 한 달에 15일 이상 최소3개월 전부터 지속되는 경우

Pathophysiology of Migraine
Trigeminovascular Migraine Pain Pathways



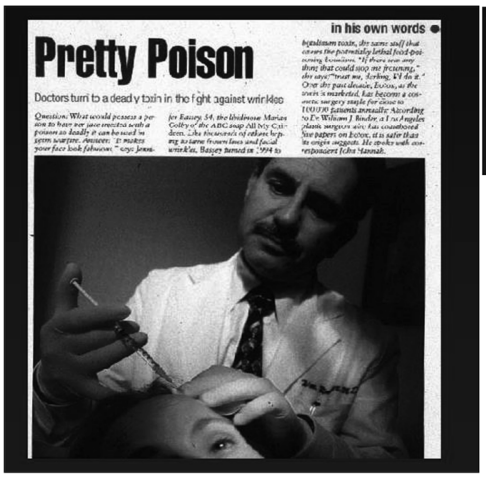
Hargreaves RJ, Shepheard SL. *Can J Neurol Sci.* 1999;26(suppl 3):S12-S19.

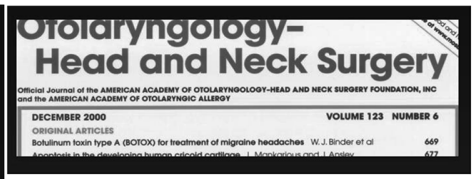
Botox in CM
from concept to clinical study

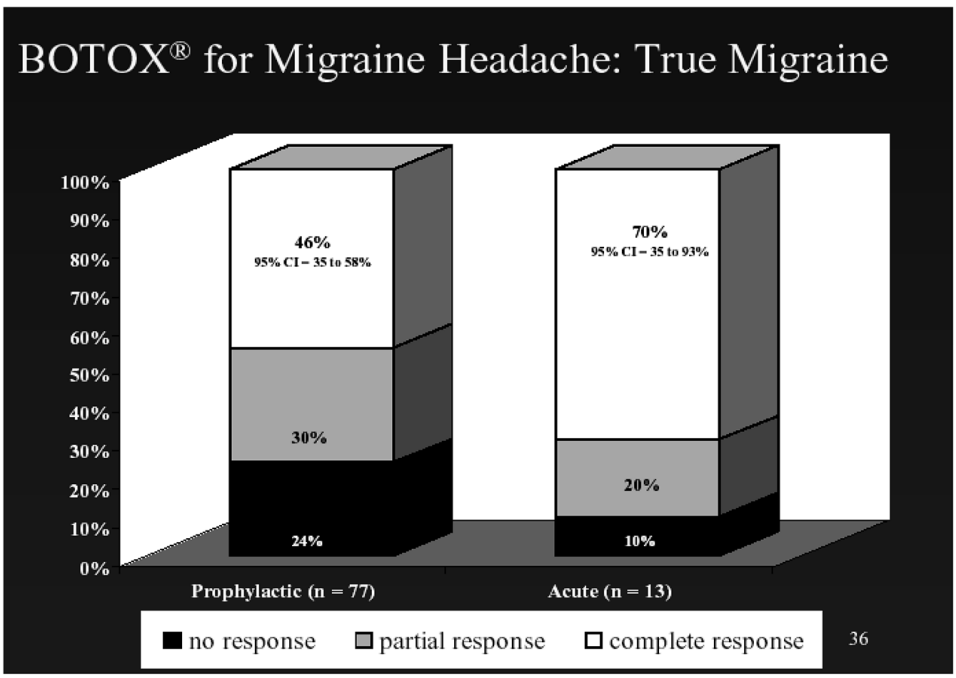


1. Keen M *et al. Plast Reconstr Surg* 1994;94:94–9. **2.** Zwart JA *et al. Headache* 1994;34:458–62. **3.** Binder W *et al. Mov Disord* 1998;13(Suppl 2):241. **4.** Relja MA *et al. Neurology* 1999;52(Suppl 2):A203 P03.035. **5.** Binder WJ *et al. Otolaryngol Head Neck Surg* 2000;123:669–76. **6.** Silberstein S *et al. Headache* 2000;40:445–50. **7.** Mathew NT *et al. Headache* 2005;45:293–07. **8.** Dodick DW *et al. Headache* 2005;45:315–24. **9.** Dodick DW *et al. Headache* 2010;50:921–36. **10.** Allergan Summary of Product Characteristics. Allergan Ltd. 2011. **11.** Aurora SK *et al. Headache* 2011;51:1358–73.

Botulinum toxin A therapy for migraine prophylaxis starts from retrospective study…..
by WJ Binder, 1992







n=77

Type of treatment administered and migraine classification of patients treated with BOTOX (n=106)

Migranine Classification*	Prophylatic	Acute	Both prophylactic and acute
True	69	2	8
Possible	15	2	1
Non	9	0	0

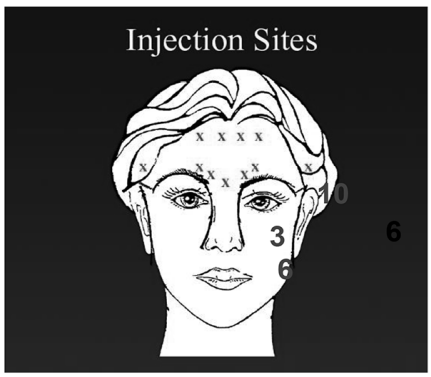
- Based on self-reported baseline headache histories and International Headache Society criteria for migraine aura.
  Mean dose 31.0 u (5-110 u)
- Result in true migraine
  Acute TX : 70% complete response 1 to 2 hrs after TX(7/10)
  Prophylactic TX : 51% complete response (dm 4.1 mo)
  38% Partial response (>50%) (dm 2.7 mo)

Why it is unlikely pain relief is a placebo effect?

- Binder's patients were not expecting change in their migraine pattern
- Sustained effect
- Central desensitization effect (aura, N/V, allodynia)

BOTOX® for Migraine: Study Design (Allergan Sponsored)

- Randomized, multicenter, double-blind, vehicle-controlled, parallel-group study
- 3 pericranial muscle regions injected
  - Total of 11 injection sites
- 3 dose groups: vehicle, 25 U BOTOX®, 75 U BOTOX®



(Silberstein, *headache*, 2000) **n=123, 25U/75U**

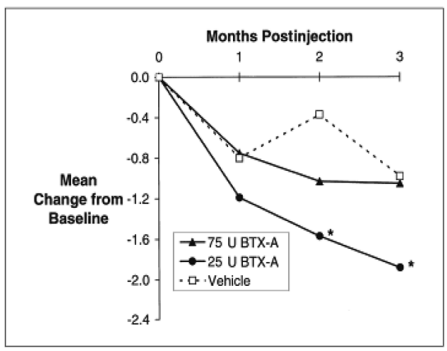


Fig 2.—Mean decrease from baseline in the number of moderate-to-severe migraines per month. Asterisks indicate that the 25-U BTX-A group was significantly different from the vehicle group at 2 and 3 months postinjection ($P \leq .042$).

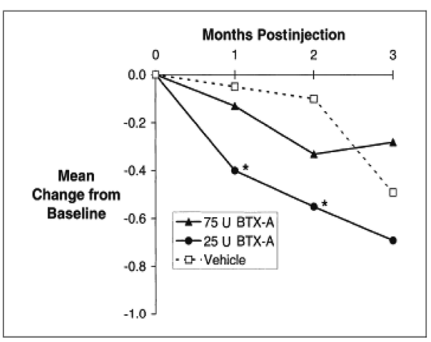


Fig 4.—Mean decrease from baseline in the maximum severity of migraines (rated on a 0-to-3 scale). Asterisks indicate that the 25-U BTX-A group was significantly different from the vehicle group at 1 and 2 months postinjection ($P \leq .029$).

△ **Because of lower frequency (#2-8/Mo) of migraine at baseline (except GA) Vomiting improved**

(Silberstein headache, 2000)

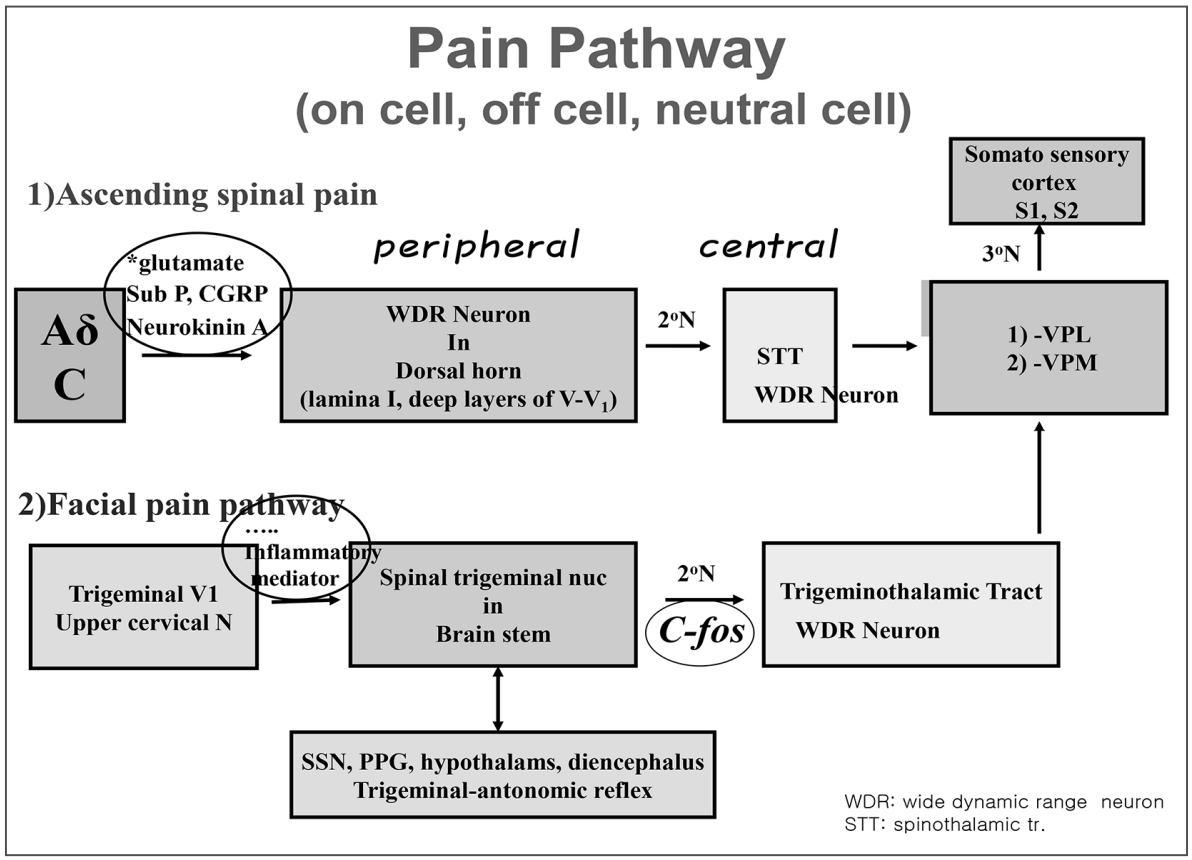
Evidence: Mechanism of action of BTX A in relieving headache

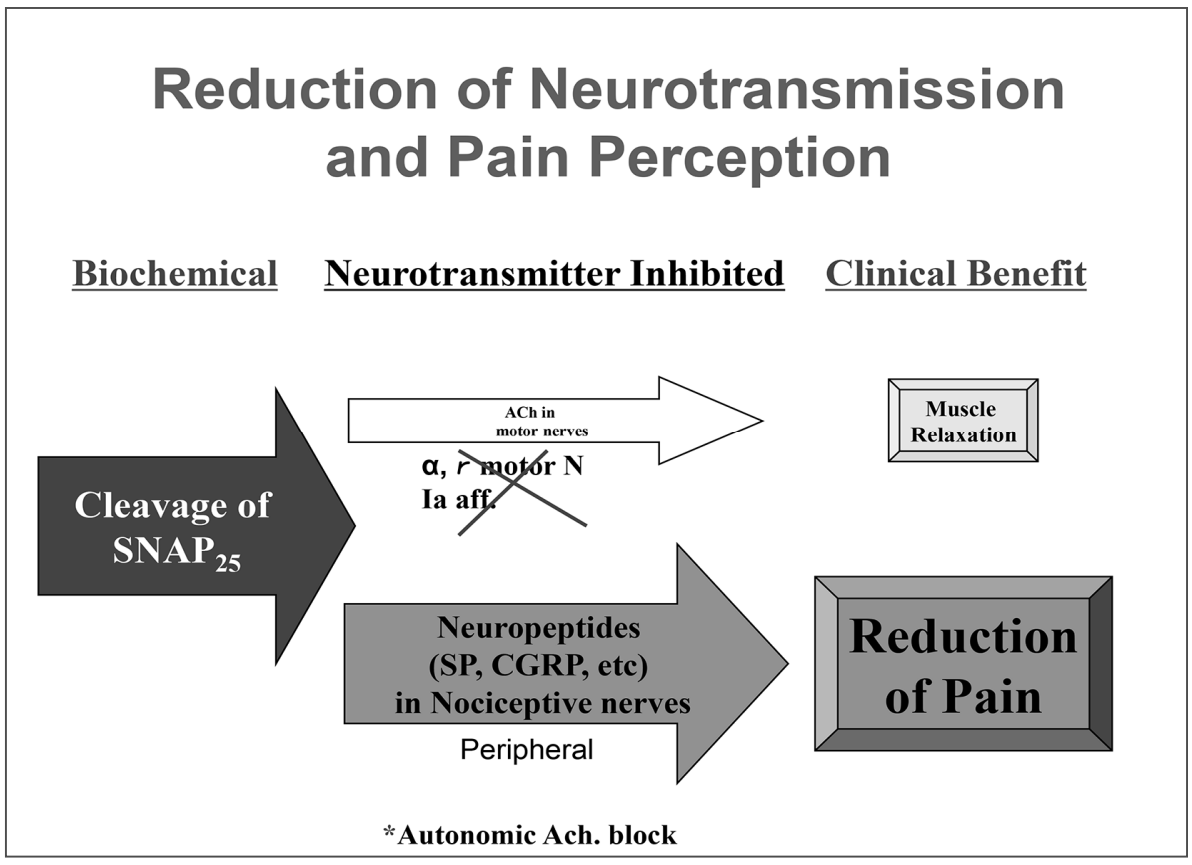
Hypothesis
Modulating trigemino vascular reflex
not only muscle relaxation itself

M.Y. Park
2001. seoul

Dual effect

1. **Peripheral antinociception**
2. **Indirect central desensitization**


Pain Pathway
(on cell, off cell, neutral cell)
1)Ascending spinal pain
peripheral
central
Somato sensory cortex S1, S2
3ºN
*glutamate
Sub P, CGRP
Neurokinin A
Aδ
C
WDR Neuron In Dorsal horn (lamina I, deep layers of V-V1)
2ºN
STT
WDR Neuron
1) -VPL
2) -VPM
2)Facial pain pathway
…..
Inflammatory mediator
Trigeminal V1
Upper cervical N
Spinal trigeminal nuc in Brain stem
2ºN
C-fos
Trigeminothalamic Tract
WDR Neuron
SSN, PPG, hypothalams, diencephalus
Trigeminal-antonomic reflex
WDR: wide dynamic range neuron
STT: spinothalamic tr.


Reduction of Neurotransmission and Pain Perception
Biochemical
Neurotransmitter Inhibited
Clinical Benefit
Cleavage of SNAP25
ACh in motor nerves
α, γ motor N
Ia aff.
Muscle Relaxation
Neuropeptides (SP, CGRP, etc) in Nociceptive nerves
Peripheral
Reduction of Pain
*Autonomic Ach. block

2002년 11월 영남대학교의료원 신경과 Daegu

Objectives

To assess the safety & efficacy in the prophylaxis of migraine

Subjects & Methods

N=19(M:F=7:12), mean age 41yrs (18-61)
Ds duration 14yrs(5.1)
*Migraine with aura : without aura = 8 :11(IHS)
BOTOX®(Allergan) : 48 IU(±5.5)
Follow up: Every 4wks for 24wks
Data analysis : Stata ver. 6.0
Generalized estimating equation method

(박미영, 대한신경과학회, 2002)

Evaluation parameters

Reducing or eliminating daily chronic headache, medications or either prophylaxis/or acute treatment

Frequency change
Severity change
Reduction of medication
→ **Global Assesment of Improvement (0-100%)**

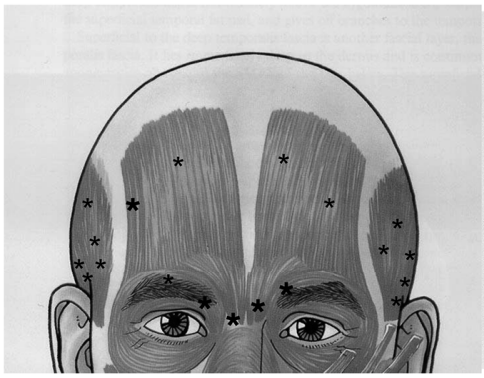
Aura
Nausea/Vomiting
Side effects

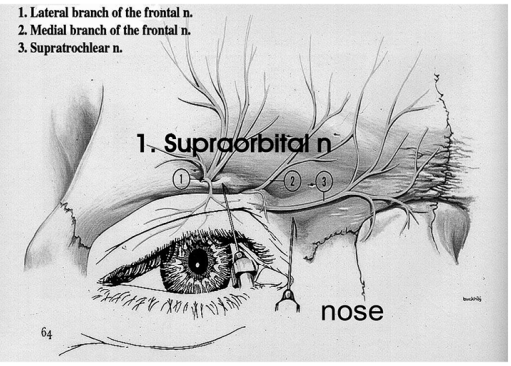
M.Y. Park
2001. seoul

Method

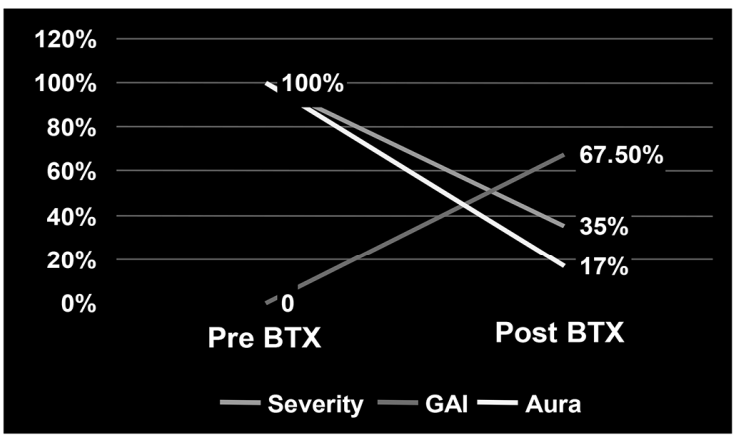
- **No established or standardized methodology**
- **Approach (Andrew, 2003)**
  - **fixed site**
  - **followed the - pain**
  - **combination**

Injection site





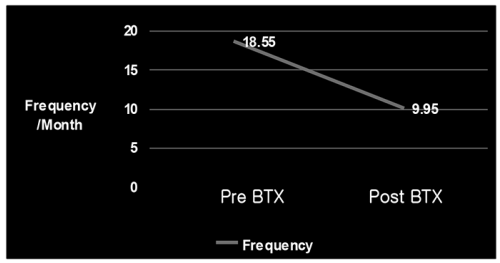
Results at 12wk



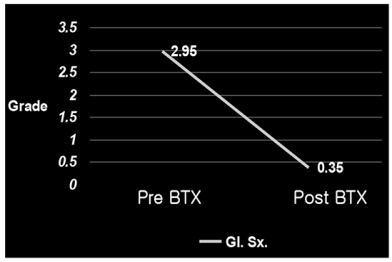
P<0.000

(박미영, 대한신경과학회, 2002)

Results at 12wk



P<0.05



P<0.000

(박미영, 대한신경과학회, 2002)

Results (~pilot)

sex	age	duration of disease(yrs)	cafergot overuse	change of frequency	change of severity	aura	N/V(0-4)	GAI(0-100%)
F	18	5	+	15 → 12	-30%	-	2 →0	30%
M	48	10	+	20 → 7	-50%	+ → -	3 →1	60%
M	43	20	+	3/D →↓	-20%	-	4 → 0	20%
M	34	20	+++	0	0	+ → +	2 → 2	0
M	50	2	-	1/D →	-70%	+ → -	1 → 0	60%
F	61	30	-	1/D →	-20%	+ → -	2 → 1	20%
F	52	27	-	4/D →1/D	-60%	± → -	3 → 0	60%
F	50	20	-	20 → 10	-30%	-	3 → 2	50%
M	57	15	-	54 → 18	-70%	-	3 → 0	80%
M	32	17	-	8 →5	-90%	-	3 →0	90%
M	21	10	-	8 → 5	-80%	+ →-	2 →0	90%
F	29	61	-	8 →0	-90%	-	2 → 0	100%
F	51	20	-	2 → 0	-90%	+ →-	4 → 0	100%
M	18	5	-	12 → 3	-90%	+ →-	3 → 0	100%

Elimination : 21%(3/14)
Improvement >50% : 50%(7/14)
Improvement <50% : 21%(3/14)
No response : 7%(1/14)

4 cases of side effect

M.Y. Park
2001. seoul

Interpretation, Patient selection

- **Cafergot addictor**
- **Associated nausea improving**
- **Elimination (but migraineous episodes without pain)**
- **Lesser frequency → more effective to BTX TX**
- **Mixed headache**
- **1yr. followed Pt.**

M.Y. Park
2001. seoul

Adverse effects &…

- Blepharoptosis
- Lateral eye brow elevation (Mephisto sign)
- Weakness sensation of chewing
- Frontal heaviness
- Headache

"Mephisto sign" 일명 사무라이 눈썹

Conclusion

BTX A is shown to be benificial therapeutic agent in migraine, but

- ***Optimal dose, site of injection, injection interval &***
- ***Appropriate patient selection characteristics should be further investicated***

PREEMPT STUDY 2011 for CM

Phase 3 **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy

- **155-195u**
- **Phase Ⅲ**
- **1.384 subjects,** 122 center north America, EU
- **injection every 12WK: 2cycle +3cycle open label**
- **HIT-6 -** severe (≥60) HIT-6 category score
- **MSQ v.21 (HRQoL)** 3 domain scores

➡ **Class 1A**

HIT: Headache Impact Score
MSQ: Migraine-specific quality-of-life questionnaire

PREEMPT 2010 Pooled data

24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase (a Phase III study)

PREEMPT I

- Injections every 12 weeks of onabotulinumtoxin A (155 U–195 U; n=341) or placebo (n=338) (two cycles).
- The primary endpoint: mean change from baseline in headache episode frequency at week 24. – No significant
- the secondary endpoints: headache days (p=.006) and migraine days((p=0.002) reduction

Cephalalgia 30(7) 793–803 Aurora et al.

PREEMPT II

- a phase 3 study, with a 24-week, double-blind, placebo-controlled phase, followed by a 32-week, open-label phase.
- Subjects were randomized (1:1) to injections of onabotulinumtoxin A (155U–195U; n=347) or placebo (n=358) every 12 weeks for two cycles.
- The primary efficacy endpoint: mean change in headache days per 28 days from baseline to weeks 21–24 post-treatment.
- The secondary efficacy endpoint: frequency of migraine days, frequency of moderate/severe headache days, monthly cumulative headache hours on headache days, proportion of patients with severe Headache Impact Test (HIT)-6 score, frequency of headache episodes, acute headache pain medication intakes, HIT-6 score, MSQ v2.1, HIS.

Cephalalgia 30(7) 804–814, Diener et al. 2010

Efficacy of onabotulinumtoxinA at week 24 - PREEMT trial II

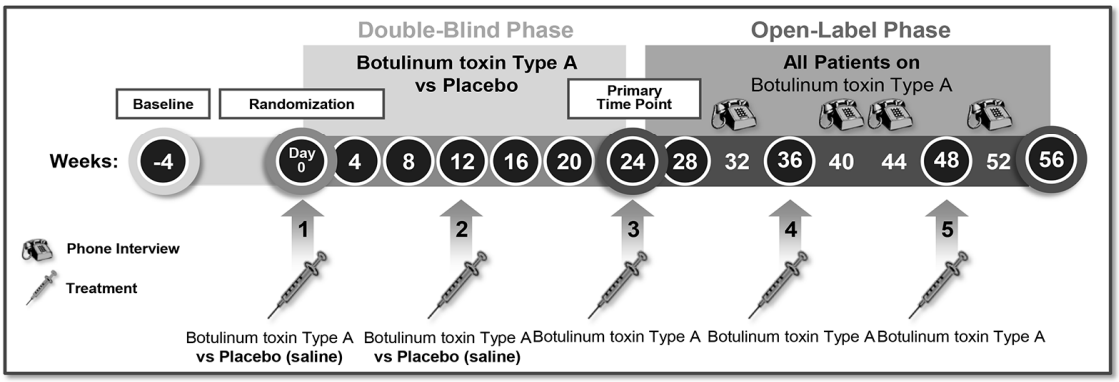
Endpoint	OnabotulinumtoxinA ($n=347$)	Placebo ($n=358$)	Mean intergroup difference‖	p value‖
Change from baseline in frequency of headache days*†	−9.0	−6.7	−2.3 (−3.25, −1.31)	<.001
Change from baseline in frequency of migraine days†‡	−8.7	−6.3	−2.4 (−3.31, −1.36)	<.001
Change from baseline in frequency of moderate/severe headache days†	−8.3	−5.8	−2.5 (−3.37, −1.48)	<.001
Change from baseline in cumulative total headache hours on headache days†	−132.4	−90.0	−42.4 (−58.23, −21.05)	<.001
% Patients with severe (≥60) HIT-6 score†§	66.3	76.5	−10.2 (−16.9, −3.6)	.003
Change from baseline in frequency of headache episodes†	−5.3	−4.6	−0.7 (−1.65, −0.33)	.003
Change from baseline in total HIT-6 scores†§	−4.9	−2.4	−2.5 (−3.54, −1.55)	<.001
Change from baseline in frequency of acute headache pain medication intakes (all categories)	−9.9	−8.4	−1.5 (−3.77, 0.49)	.132
Change from baseline in frequency of triptan intake	−3.0	−1.7	−1.3 (−2.24, −0.6)	<.001

HIT, Headache Impact Test. *Primary efficacy endpoint. †Significant between-group differences favouring onabotulinumtoxinA. ‡International Classification of Headache Disorders, II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine) (1). §Scores of 36–49 indicate little or no impact; 50–55, some impact; 56–59, substantial impact; ≥60, severe impact. ‖The 95% confidence intervals and p values are adjusted for baseline and for medication overuse stratification.

Cephalalgia 30(7) 804–814, Diener et al. 2010

PREEMPT: Study design of two phase 3 studies of chronic migraine patients

- Largest clinical program on Chronic Migraine sufferers (1384 patients)
  - 122 sites in North America and Europe; 11 sites in Canada
  - 24주 무작위 이중맹검 위약대조 후 32주 개방표지 3상 임상연구

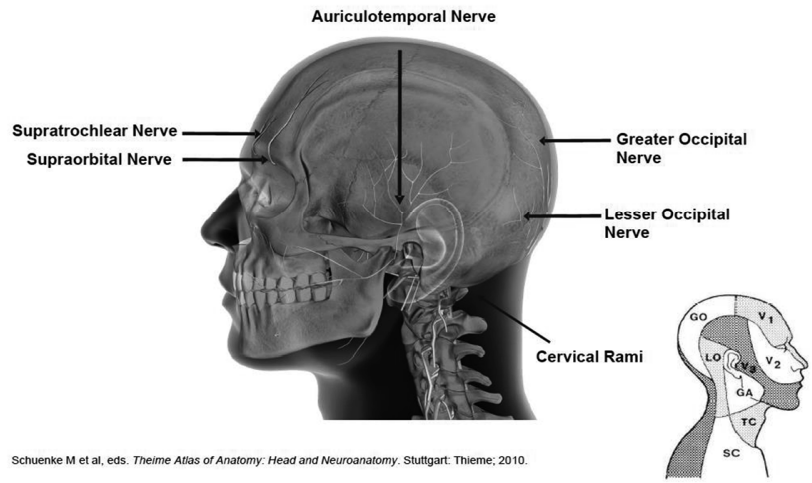


- Headache symptoms and medications were recorded in a daily telephone diary

Blumenfeld et al. *Headache*. 2010;50:921-936..

Injection site

Distribution & areas innervated by of trigeminal sensory system



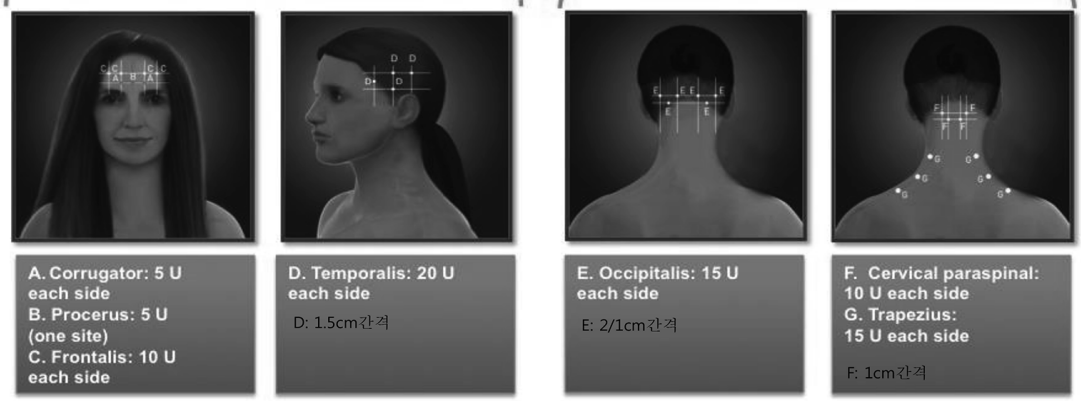
Schuenke M et al, eds. *Theime Atlas of Anatomy: Head and Neuroanatomy*. Stuttgart: Thieme; 2010.

Injection Paradigm

Order of injection and patient position : FSFD

- The anatomic injection sites follow distributions and areas innervated by the trigeminal nerve complex

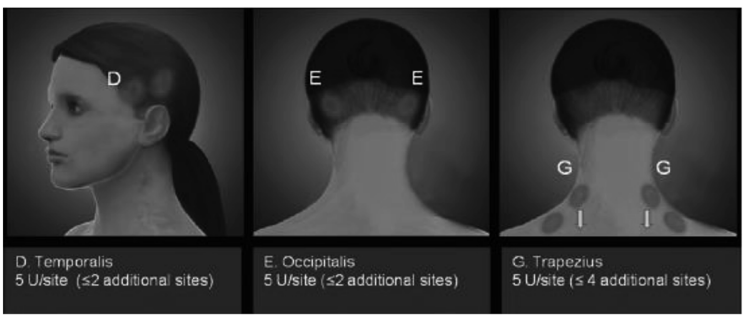
Supine **Sitting**



0.1 mL = (5 U/site). 2ml 희석 30G 0.5inch needle
Blumenfeld AM et al. Headache 2010;50:1406-1418.

Total 31points 155 U

Follow-the-pain muscle areas of maximal tenderness and/or pain.



Total 39points 195 U

Pooled baseline demographics

	Botulinum toxin Type 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 HA days (SD)	20 (4)	20 (4)
Mean migraine days (SD)	19 (4)	19 (4)
Mean moderate/severe HA days (SD)	18 (4.1)	18 (4.3)
Mean cumulative hours of HA occurring on HA days (SD)	296 (117)*	281 (115)*
Mean HIT-6 score	66	65
% Patients with severe (≥ 60) HIT-6 score	94	93
Mean HA episodes (SD)	12 (5)*	13 (6)*
Mean migraine episodes (SD)	11 (5)*	12 (5)*
% 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.

Pooled efficacy of Botulinum toxin Type A at week 24 (primary time point)

Endpoint, Mean Change From Baseline	Botulinum toxin Type A (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 triptan use	-3.2	-2.1	<0.001

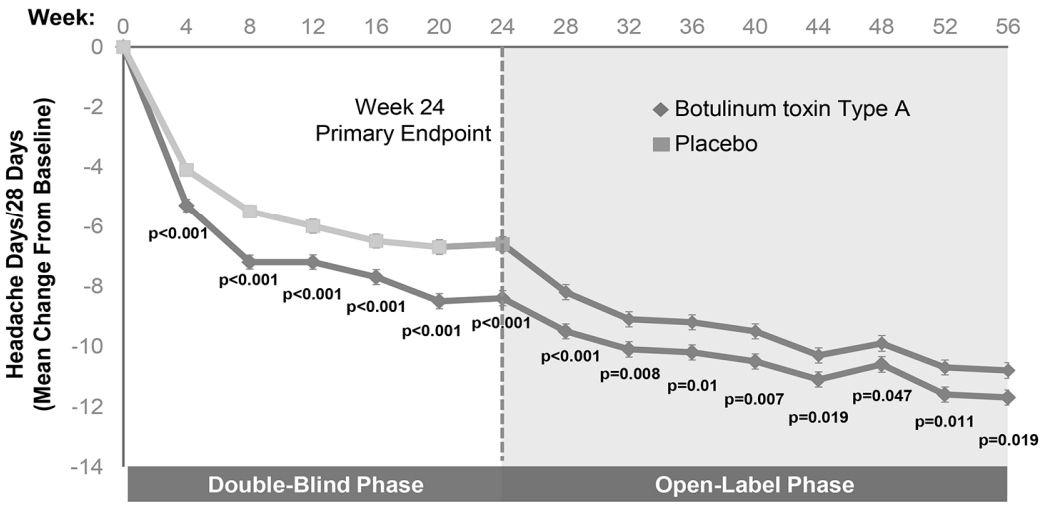
Botulinum toxin Type A was statistically significantly more effective than placebo in reducing mean frequency of headache days at every visit in the double-blind phase starting at the first post-treatment study visit (Week 4).
*p values are adjusted for baseline and for medication overuse stratification.

HA = headache; HIT = Headache Impact Test.

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

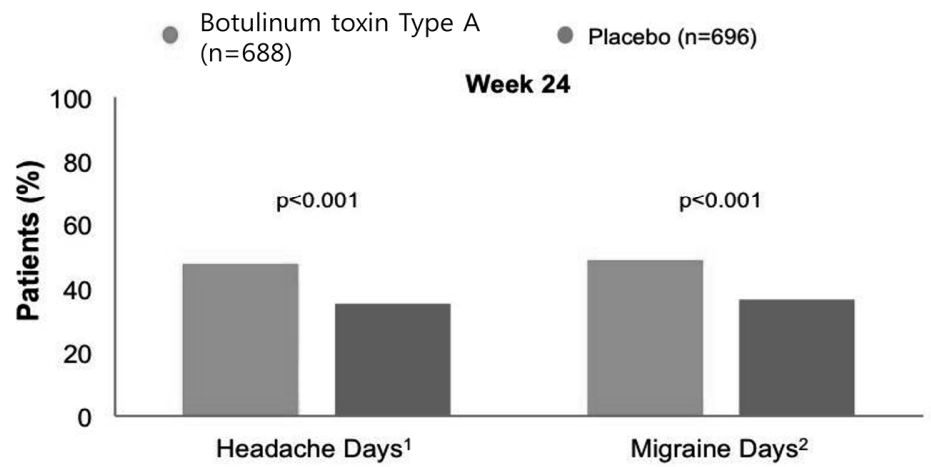
PREEMPT pooled analysis: Change in headache days – primary

~70% of patients* achieved ≥50% reduction in headache days at 56 weeks[1]



*Patients who received Botulinum toxin Type A throughout the 56-week treatment program.
Mean ± standard error.
The double-blind phase included 688 subjects in the Botulinum toxin Type A group and 696 in the placebo group.
Headache days at baseline: 19.9 Botulinum toxin Type A group vs 19.8 placebo group, p=0.498.
1.Aurora et al. Headache. 2011 51(9):1358-7

PREEMPT pooled analysis: ≥50% Decrease from baseline in headache days & migraine days

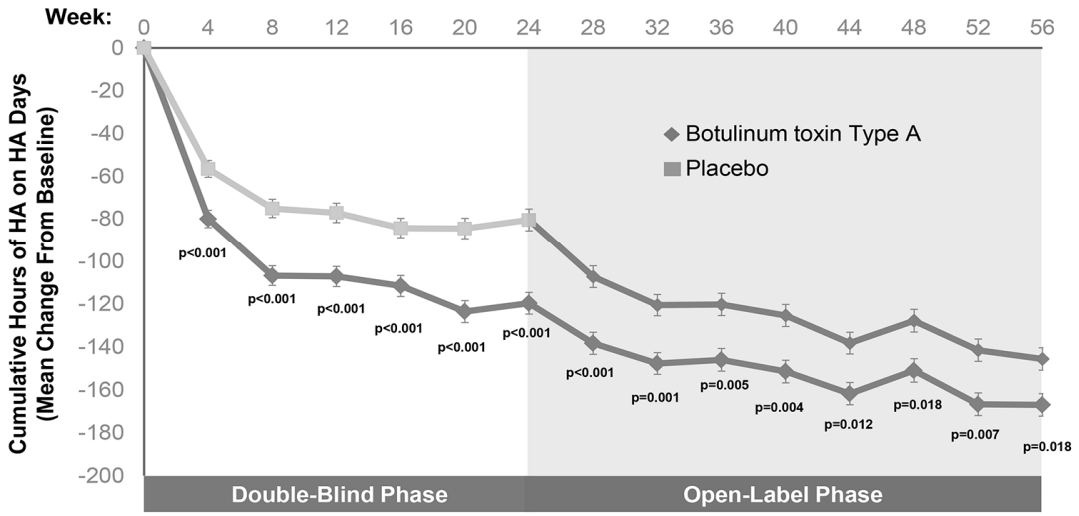


Headache days at baseline: 19.9Botulinum toxin Type A group vs 19.8 placebo group, p=0.498.
Migraine days at baseline: 19.1Botulinum toxin Type A group vs 18.9 placebo group, p=0.328.

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

PREEMPT pooled analysis:

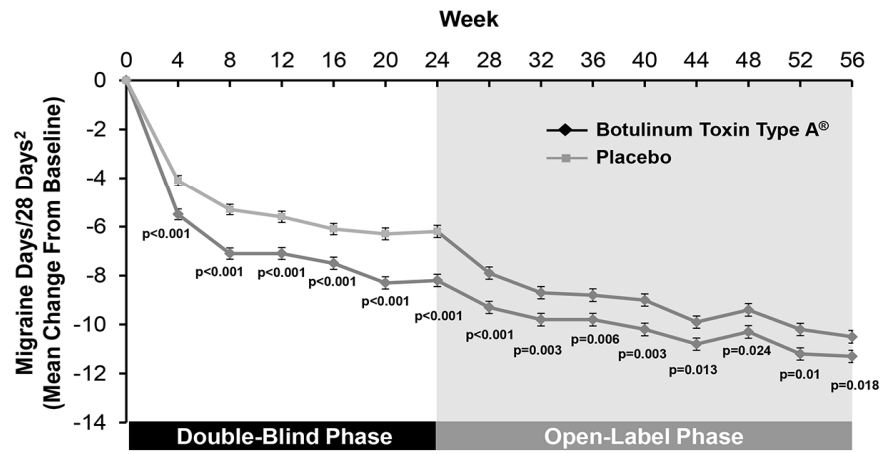
Botulinum toxin Type A reduced cumulative headache hours on headache days



Mean ± standard error.
The double-blind phase included 688 subjects in the Botulinum toxin Type A group and 696 in the placebo group.
Cumulative hours of headache at baseline: 295.9 Botulinum toxin Type A group vs 281.2 placebo group, p=0.021.
HA = headache.
Aurora et al. Headache. 2011 51(9):1358-7

~70% of Patients* Achieved ≥50% Reduction in Headache Days at 56 Weeks[1]

Patients Treated With Botulinum Toxin Type A Averaged 8 Fewer Migraine Days/Month Compared to Baseline at Week 24



Mean ± standard error.
The double-blind phase included 688 subjects in the botulinum toxin type A group and 696 in the placebo group.
Migraine days at baseline: 19.1 botulinum toxin type A group vs 18.9 placebo group, p=0.328.
1. Data on file. Allergan, Inc.
2. Aurora SK et al. Presented at IHC 2009.

PREEMPT: Summary of adverse events pooled data, double-blind phase (%)

	Botulinum toxin Type A (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 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: Botulinum toxin Type A is a well-tolerated treatment for chronic migraine

- No new treatment-related AEs were identified
- Most AEs were mild or moderate in severity and resolved without sequelae

	Botulinum toxin Type A (n = 687)	Placebo (n = 692)
Neck pain	60 (8.7)	19 (2.7)
Muscular weakness	24 (5.5)	2 (0.3)
Headache	32 (4.7)	22 (3.2)
Migraine	26 (3.8)	18 (2.6)
Musculoskeletal stiffness	25 (3.6)	6 (0.9)
Eyelid ptosis	25 (3.6)	2 (0.3)
Injection-site pain	23 (3.3)	14 (2.0)
Myalgia	21 (3.1)	6 (0.9)
Musculoskeletal pain	18 (2.6)	10 (1.4)
Facial paresis	15 (2.2)	0 (0.0)

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

PREEMPT subgroup analysis: CM+MO
Botulinum toxin Type A is an effective treatment for chronic migraine patients who overuse acute pain medications

Change from baseline in headache characteristics, impact and health-related quality of life at **Week 24** in the chronic migraine with acute headache medication overuse subgroup.

Mean change from baseline, variable	CM + MO		
	OnabotulinumtoxinA (n = 445)	Placebo (n = 459)	p value[a]
Frequency of headache days (SE)	−8.2 (0.30)	−6.2 (0.31)	<0.001
Frequency of migraine[b] days (SE)	−8.1 (0.30)	−6.0 (0.31)	<0.001
Frequency of moderate/severe headache days (SE)	−7.7 (0.29)	−5.7 (0.31)	<0.001
Total cumulative hours of headache on headache days (SE)	−114.5 (5.77)	−70.8 (6.08)	<0.001
% patients with severe (≥60) HIT-6 score[c,d]	71.0	81.9	<0.001
Frequency of headache episodes (SE)	−5.4 (0.26)	−5.1 (0.25)	0.028
Frequency of migraine[b] episodes (SE)	−5.1 (0.25)	−4.8 (0.25)	0.018
Frequency of AHM intakes[e]	−13.1 (0.90)	−11.8 (0.89)	0.210
Total HIT-6 score[c]	−4.7[f]	−2.2[f]	<0.001
% patients achieving ≥5-point reduction in HIT-6 score[c,d]	38.7	23.3	<0.001
MSQ score[g]: Role function-restrictive	16.9[h]	7.6[h]	<0.001
MSQ score[g]: Role function-preventive	13.9[h]	5.8[h]	<0.001
MSQ score[g]: Emotional functioning	18.3[h]	8.7[h]	<0.001

AHM = acute headache medication, HIT = Headache Impact Test, HRQoL = health-related quality of life, ICHD = International Classification of Headache Disorders, MSQ = Migraine-Specific Quality of Life questionnaire.

[a] $p \leq 0.05$ is statistically significant. The p values are adjusted for baseline.

[b] ICHD-II 1.1 (migraine without aura), 1.2 (migraine with aura), 1.6 (probable migraine) [1].

[c] HIT-6: scores 36–49 = little or no impact; 50–55 = moderate impact; 56–59 = substantial impact; 60–78 = severe impact.

[d] Statistics are raw score, not change from baseline.

[e] Intakes denote the number of times that a patient self-treated with an acute medication, not the amount of medication(s) taken. An intake occurred each time a patient sought relief, regardless of the number of medications or doses taken at the same time.

[f] Difference between the groups exceeds the established minimally important between-group difference [27].

[g] MSQ scores range from 0 (poor HRQoL) to 100 (good HRQoL).

[h] Difference between groups exceeds minimally important differences for each MSQ domain [31].

MO: medication overuse

Journal of the Neurological Sciences 331 (2013) 48–56 Stephen D. Silberstein et al.

Treatment Effect Size Compared to Other Treatments

	50% Responder Rate (Active / Placebo); NNT	Discontinuation Due to Adverse Events	Migraine/ Migrainous Days; Absolute Between-Group Difference
Botulinum Toxin Type A[1]	**47% / 35%* 8**	**3.8%**	**-8.2 (2.0)**
Topiramate[2,3]	**37% / 29%* 12.5**	**10.9%**	**-6.4 (1.7)**

*≥50% reduction in mean monthly migraine days.
These were not comparison studies. The topiramate data come from a double-blind study assessing topiramate efficacy in Chronic Migraine patients, and the **botulinum toxin type A** data come from the pooled results of the PREEMPT studies.

NNT = Number Needed to Treat.

1. Dodick DW et al. *Headache.* 2010:50:921-963.
2. Silberstein SD et al. *Headache.* 2009;49:1153-1162.
3. Silberstein SD et al. *Headache.* 2007:47:170-180.

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Blumenfeld *et al. BMC Neurology* (2015) 15:100
DOI 10.1186/s12883-015-0353-x

BMC Neurology

STUDY PROTOCOL Open Access

Unmet clinical needs in chronic migraine: Rationale for study and design of COMPEL, an open-label, multicenter study of the long-term efficacy, safety, and tolerability of onabotulinumtoxinA for headache prophylaxis in adults with chronic migraine

Andrew M. Blumenfeld[1*†], Sheena K. Aurora[2*†], Karen Laranjo[3] and Spyros Papapetropoulos[4]

Study objectives for COMPEL

Primary Objective

To assess mean change from baseline in the frequency of headache days per 28-day period at 108 weeks (following 9 treatments) using a patient diary completed via IVRS.

Secondary Objectives

To assess mean change from baseline in the frequency of headache days for the 28-day period ending at 60 weeks (following 5 treatments).

To assess the efficacy of onabotulinumtoxinA treatment for CM in adult patients as measured by the mean change from baseline in total HIT-6 score over a 4-week period at 108 weeks (following 9 treatments) and at 60 weeks (following 5 treatments).

To evaluate the long-term safety and tolerability (9 treatment cycles) of onabotulinumtoxinA for CM in adult patients.

CM = chronic migraine; HIT-6 = Headache Impact Test-6; IVRS = interactive voice response system

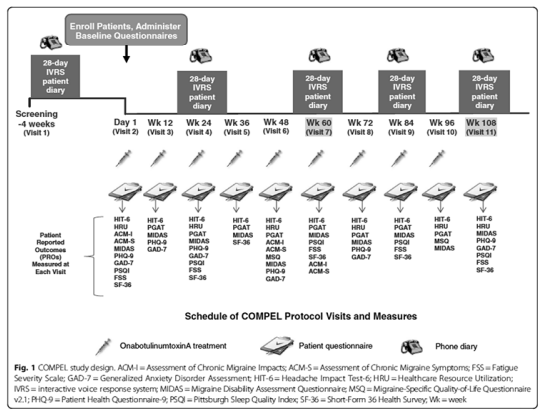
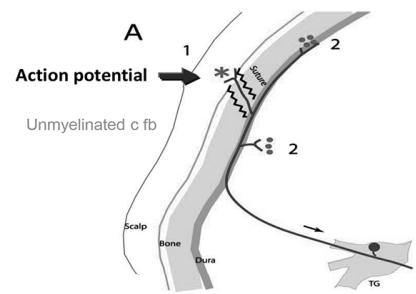


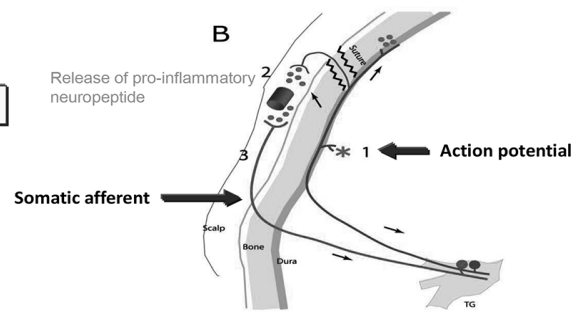
Fig. 1 COMPEL study design. ACM-I = Assessment of Chronic Migraine Impacts; ACM-S = Assessment of Chronic Migraine Symptoms; FSS = Fatigue Severity Scale; GAD-7 = Generalized Anxiety Disorder Assessment; HIT-6 = Headache Impact Test-6; HRU = Healthcare Resource Utilization; IVRS = interactive voice response system; MIDAS = Migraine Disability Assessment Questionnaire; MSQ = Migraine-Specific Quality-of-Life Questionnaire v2.1; PHQ-9 = Patient Health Questionnaire-9; PSQI = Pittsburgh Sleep Quality Index; SF-36 = Short-Form 36 Health Survey; Wk = week

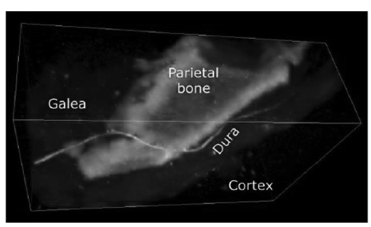
Meningeal sensory Fibers Innervate Extracranial Subcutaneous Tissue and Calvarium

Extracranial origin of intracranial pain



Intracranial origin of extracranial pain





Kosaras B, et al. J Comp Neurol 2009;515:331–348

Hypothesis
OnabotulinumtoxinA antinocicepton

- The exact mechanism of onabotulinumtoxinA in antinociception has not been fully elucidated
- Animal and human studies indicate that onabotulinumtoxinA inhibits the release of nociceptive mediators[1,2,5]:
  - cGRP
  - Glutamate
  - Substance P
- Blocking release of these neurotransmitters inhibits neurogenic inflammation; this, in turn, inhibits peripheral sensitization of nociceptive nerve fibers[1,5,6]
- As a result, peripheral pain signals to the central nervous system are reduced and, indirectly, central sensitization is blocked[1,6]

cGRP = calcitonin gene-related peptide.

1. Aoki KR. Headache. 2003;43(suppl 1):S9-S15. 2. Aoki KR. Neurotoxicology. 2005;26:785-793.
3. Cui M. Pain. 2004;107:125-133. 4. Durham PL. Headache. 2004;44:35-42.
5. Gazerani P. Pain. 2006;122:315-325. 6. Gazerani P. Pain. 2009;141:60-69.

Summary : BOTOX is efficacious and well tolerated in chronic migraine

- BOTOX is the proven preventive medication in the treatment of Chronic Migraine
- In PREEMPT clinical trials, treatment with BOTOX resulted in highly significant improvement versus placebo for multiple headache symptom measures in CM patients
- In the PREEMPT clinical trials, treatment with 155U to 195U of BOTOX every 12 weeks was found to be safe and well tolerated with low discontinuation rates due to AEs
  - Serious AEs were reported in 4.8% of BOTOX patients and 2.3% of placebo patients
  - Most BOTOX treatment-related AEs are transient and mild to moderate in severity
  - BOTOX is a focal treatment; systemic side effects and drug interactions are rare

However, a few considerations remain need to be researched in practice

Dodick DW et al. *Headache*. 2010; 50:921- 936.
Aurora et al. Headache. 2011 51(9):1358-7
Blumenfeld AM et al. Headache 2010;50:1406-1418