Role of Botulinum toxin for chronic migraine treatment

肉毒桿菌於慢性偏頭痛的治療

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Agenda

- Overview of chronic migraine
- Clinical data on botulinum toxin in patients with headache disorders
- Mechanism of action of BoNT/A in migraine
- My Personal experience

Chronic daily headache (CDH)

- CDH is a syndrome, not a diagnosis
- Daily or near-daily headache (≥15 days/month;≥3 months)
- The most frequent headache type in headache clinics (60%).
- Frequently with medication-overuse headache (MOH)

Chronic daily headache (CDH)

- ICHD-II (2004): defined
  - Chronic (transformed) migraine (CM)
  - Chronic tension-type headache (CTTH)
  - New daily persistent headache (NDPH)
  - Hemicrania continua (HC)
  - Medication overuse headache (MOH)
- ICHD-II revised criteria for CM & MOH ($ICHD\text{-}II_{R,}$ 2006)

ICHD-II$_R$ criteria for chronic migraine (CM)

A. Headache (TTH or migraine): ≥15 days/month for ≥ 3 months
B. has had ≥5 attacks of *Migraine without aura*
C. Headache ≥8 days/month for >3 months, fulfilling C1 or C2:
   - C1. fulfilling the criteria C & D of *migraine without aura*
   - C2. Relieved by triptan or ergot, before C1 above
D. No medication overuse and not attributed to another causative disorder

Cephalalgia 2006; 26:742-6.

Chronic Migraine

- Epidemiology
  - 2.4% general population experience CM and that 30-50% of those overuse headache medication.
  - Chronic Migraine (CM) represents ~ 90% of the cases of chronic daily headache seen in a headache specialty clinic[2]
- Annual Incidence

  -14% among patients with Episodic Migraine developed Chronic Migraine

  - age (>51 y/o, vs. <34y/o, OR=4.4)

  - Headache frequency (10-15 d/m, vs 0-4 d/m, OR=25.4)

  - Medication overuse (OR=23.4)

[1]Castillo et al. Headache 1999
[2]Bigal et al. *Headache* 2003
Pain 2003;106:81-9

Psychiatric Comorbidity among CDH Subtypes

	CDH (n=261)	CM (n=152)	CTTH (n=92)	P-value
Depressive disorders	66%	70%	59%	0.06
Any anxiety disorders	36%	43%*	25%*	<0.05
Any depressive or anxiety disorder	73%	78%*	64%*	<0.05

Headache 2000;40:818-23

Management of Chronic Migraine

- Establish the correct diagnosis
- Reduce the aggravating factors
- Treat the comorbidity such as depression
- Limit acute headache treatment
- Put on migraine preventive agents
- Neuroimaging: not mandatory
- Withdraw medication overuse (detoxification) is the most important

Saper JR, et al. *Handbook of Headache Management.* 1993.

Detoxification

-Outpatient clinic

- Prednisone (60 mg for 2 days, 40 mg for 2 days, and 20 mg for 2 days) for 6 days or the combination of
- tizanidine (slowly titration to 24mg over 4 weeks)
- long-acting NSAID

-In-patient treatment

- fail outpatient withdrawal
- have a significant complicating medical indication, such as brittle diabetes mellitus
- presence of psychiatric disturbances esp. MDD

Detoxification - In-patient treatment

- Novamin (prochlorperazine 5-10mg q8h, 63% headache free & >90% improvement)
  - Additional anti-histamine for EPS prevention
  - block the hunger for pain killer
- $MgSO_4$:
  - $MgSO_4$ 10 amp in NS 500ml iv pump for 24hr.
- Steroid
  - Methylprednisolone 100mg iv q12h(particularly if the rebound headache proves to be severe or if status migrainosus develops)
- Keto:
- 1amp iv / im q8h for pain relief

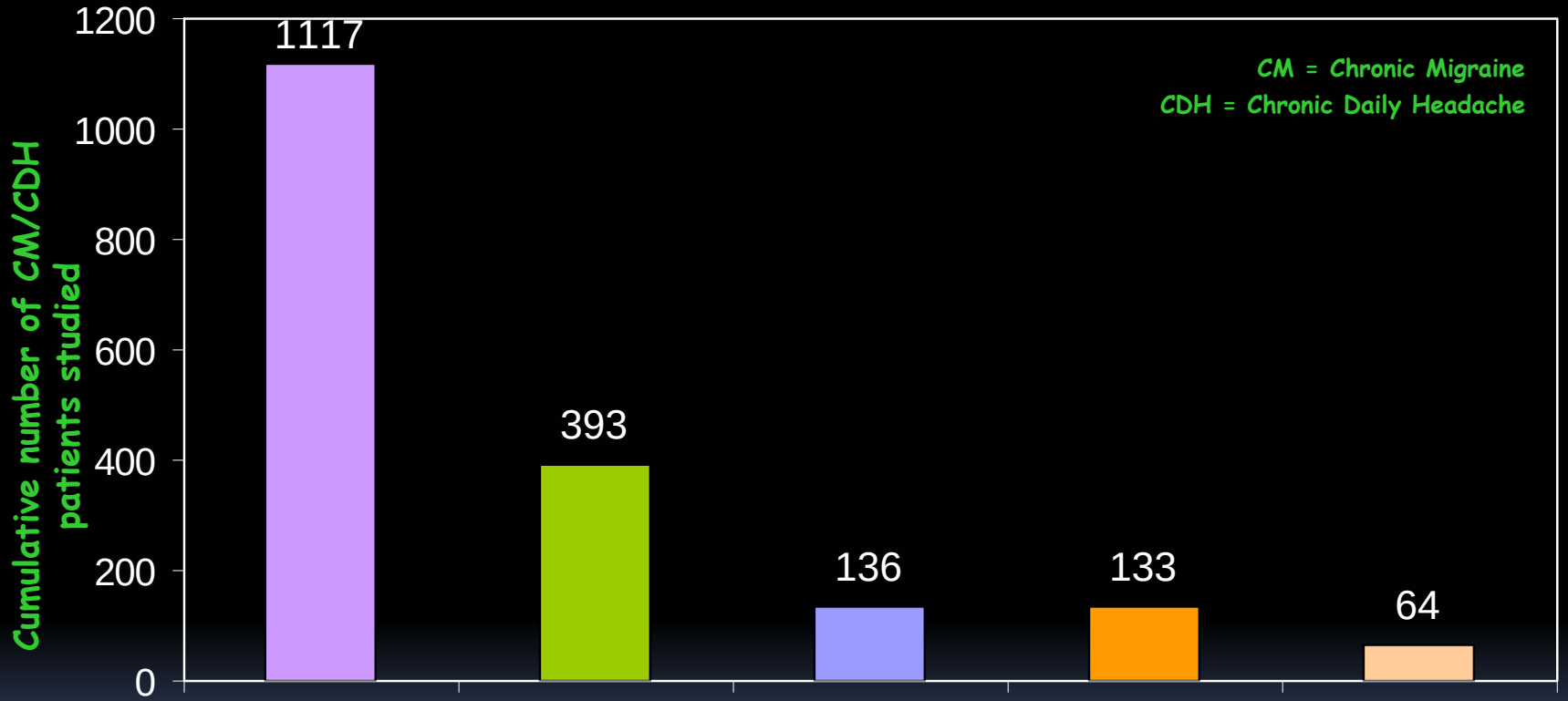
Commonly-Used Preventative Headache Medications

Preventative (prophylactic)	Episodic Migraine		Chronic Migraine/ CDH	
	Studied	FDA Approval	Studied[§]	FDA Approval
Anticonvulsants (Topiramate*‡, divalproex sodium*, gabapentin‡)	YES	YES*	YES‡	NO
Antidepressants (fluoxetine)	YES	NO	YES	NO
Beta Blockers (Propranolol, timolol)	YES	YES	NO	NO
Botulinum Toxins (BOTOX®)	YES	NO	YES	NO
Calcium Channel Blockers	YES	NO	NO	NO
Ergot Derivatives	YES	NO	NO	NO
NSAID's	YES	NO	NO	NO
α-2 Agonists (Tizanidine)	YES	NO	YES	NO

[§]Studied in double-blind, placebo-controlled trials in chronic migraine and/or chronic daily headache

No medication is currently approved specifically for the prophylactic treatment of Chronic Migraine

Studied Chronic Migraine / Chronic Daily Headache:
Cumulative number of CM / CDH patients studied



- BoNTA
  - Mathew et al. 2005
  - Silberstein et al. 2005
  - Freitag et al. 2006
- Topiramate
  - Silvestrini et al. 2003
  - Goadsby et al. 2006
  - Silberstein et al. 2006
- Tizanidine
  - Saper et al. 2002
- Gabapentin
  - Spira et al. 2003
- Fluoxetine
  - Saper et al. 1994

BoNTA = BOTOX®: Allergan, Inc., Irvine, CA, USA

Topamax®: Ortho-McNeil Inc., Titusville, N.J., USA

Zanaflex®: Elan Inc. Dublin, Ireland

Neurontin®:: Pfizer Inc., New York, NY

Prozac®: Eli Lilly Inc., Indianapolis, IN

Clinical data on botulinum toxin in patients with headache disorders

Rationale for the use of BoNT/A in headache disorders

Strbismus, Blepharospasm

hemifacial spasm, dystonia..

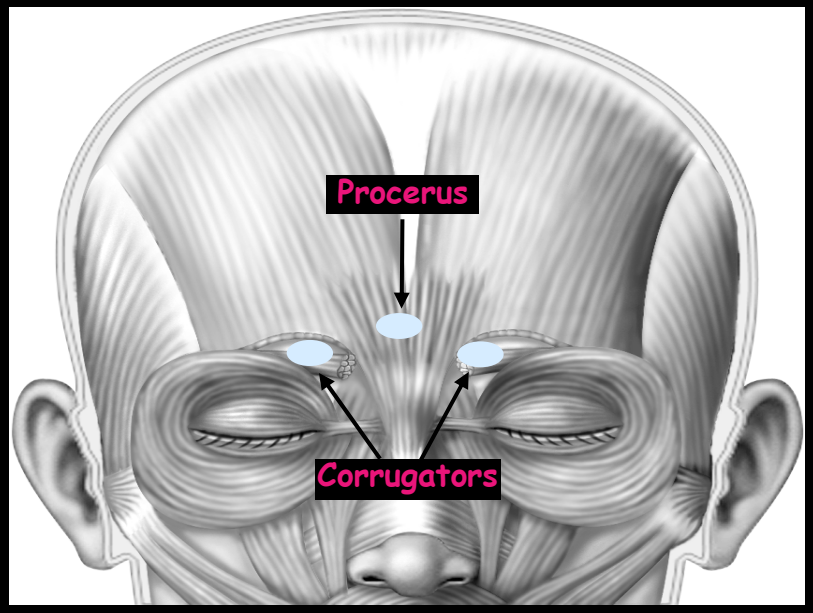
cosmetic use

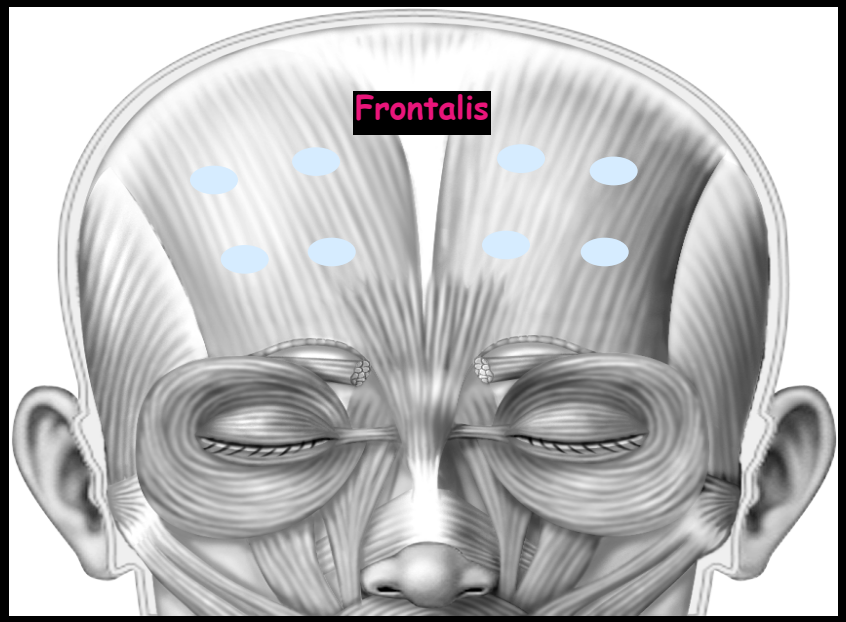
Headache/pain

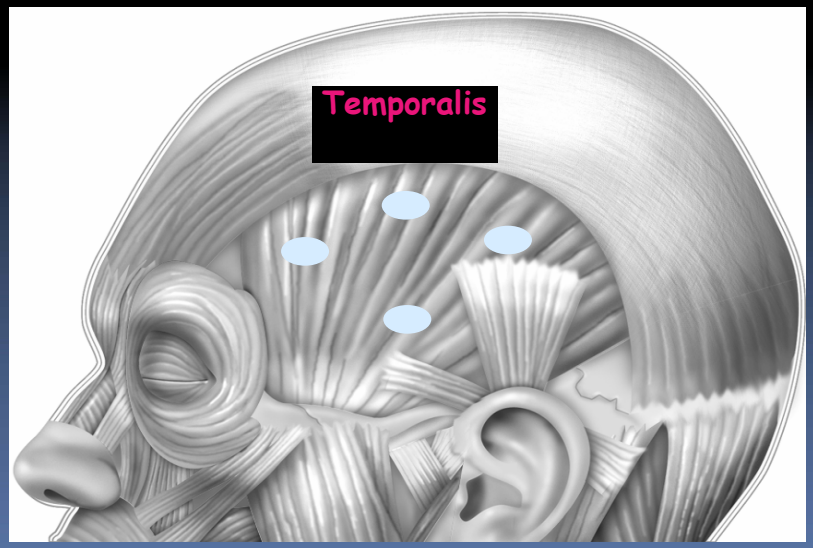
Three methods of administration of BTX

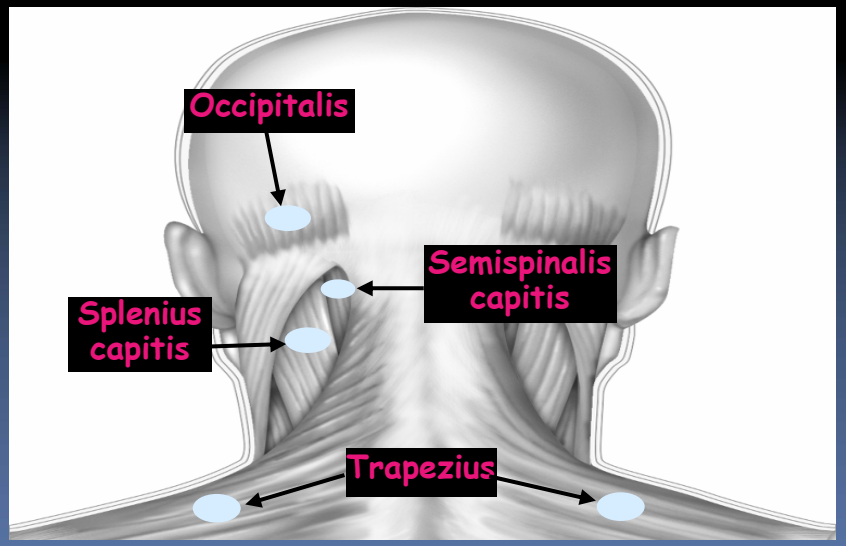
- A fixed site approach
- Follow the Pain
- A combination approach

BoNTA Studies - Injection Paradigms









Clinical data on botulinum toxin in patients with episodic tension type headache

Table 1. *Controlled studies on botulinum toxin in patients with tension-type headache*

Refs.	No. of patients	Dose [units]; distribution; formulation of BoNT/A	Rating of study (evidence class)	Result*	SAE
Rollnik et al. (2000)	21	200; FS; Dysport®	II	–	0
Schmitt et al. (2001)	60	20; FS; Botox®	II	–	0
Padberg et al. (2004)	40	100; FTP; Botox®	I	–	0
Schulte-Mattler et al. (2004)	112	500; FS; Dysport®	I	–	0
Silberstein et al. (2006)	300	50, 86, 100, 150; FS; Botox®	I	–	0

FTP Variable injection sites, "follow the pain approach"; *FS* fixed injection sites.

SAE Number of patients in that study with any serious adverse event related to botulinum toxin treatment.

* Results were judged as positive (+) only if the prospectively defined efficacy criterion was met.

J Neural Transm (2008) 115: 647–651

Clinical data on botulinum toxin in patients with CTTH

Table 1 Randomized, double-blind, placebo-controlled studies on botulinum toxin in the prophylactic treatment of tension-type headache

Study	Indication to treatment	Patients, *n*	Results compared with placebo
Göbel *et al.* (1999) [8]	Chronic tension-type headache	10	No significant reduction of pain intensity, headache hours, or use of analgesics
Smuts *et al.* (1999) [9]	Chronic tension-type headache	41	Significant reduction of headache intensity and pain-free days in month 3 compared with baseline data in group with botulinum toxin but not in placebo group
Rollnik *et al.* (2000) [10]	Chronic tension-type headache	21	No significant differences between botulinum toxin and placebo in any headache parameters
Burch *et al.* (2001) [11]	Episodic and chronic tension-type headache	41	No significant difference in headache frequency
Schmitt *et al.* (2001) [12]	Chronic tension-type headache	59	No significant differences between botulinum toxin and placebo in any headache parameters
Schulte-Mattler and Krack (2004) [13]	Chronic tension-type headache	113	No significant reduction in any efficacy endpoints
Kokoska *et al.* (2004) [14]	Chronic tension-type headache	40	No significant reduction of headache frequency; significant reduction of pain intensity
Padberg *et al.* (2004) [15]	Chronic tension-type headache	40	No significant results
Empl *et al.* (2005) [16]	Chronic tension-type headache	125	No significant results
Silberstein *et al.* (2006) [17]	Chronic tension-type headache	300	No significant difference in headache frequency (primary endpoint) for any treatment groups (treatment with 150 U was significantly inferior to placebo); significant increase in percentage of responders for 3 treatment groups

Current Opinion in Neurology 2006, 19:310–315

Clinical data on botulinum toxin in patients with episodic migraine

Table 3. *Controlled studies on botulinum toxin in patients with migraine*

Refs.	No. of patients	Dose [units]; distribution; formulation of BoNT/A	Rating of study (evidence class)	Result*	SAE
Silberstein et al. (2000)	123	25, 75; FS; Botox®	II	–**	0
Barrientos and Chana (2003)	30	50, FS; Botox®	III	–***	0
Evers et al. (2004)	60	16, 100; FS; Botox®	I	–	0
Elkind et al. (2006)	418	7.5, 25, 50; FS; Botox®	II	–	0
Relja et al. (2007)	495	75, 150, 225; FS; Botox®	I	–	0
Aurora et al. (2007)	369	110–260; FTP; Botox®	I	–	0

FTP Variable injection sites, "follow the pain approach"; *FS* fixed injection sites.
SAE Number of patients in that study with any serious adverse event related to botulinum toxin treatment.
* Results were judged as positive (+) only if the prospectively defined efficacy criterion was met.
** Significant effect only in the 25 U group but not in the 75 U group.
*** No outcome criterion was defined prospectively.

J Neural Transm (2008) 115: 647–651

Botulinum Toxin Type A as a Migraine Preventive Treatment

Headache 2000;40:445-450

Stephen Silberstein, MD; Ninan Mathew, MD; Joel Saper, MD; Stephen Jenkins, MD; for the BOTOX® Migraine Clinical Research Group

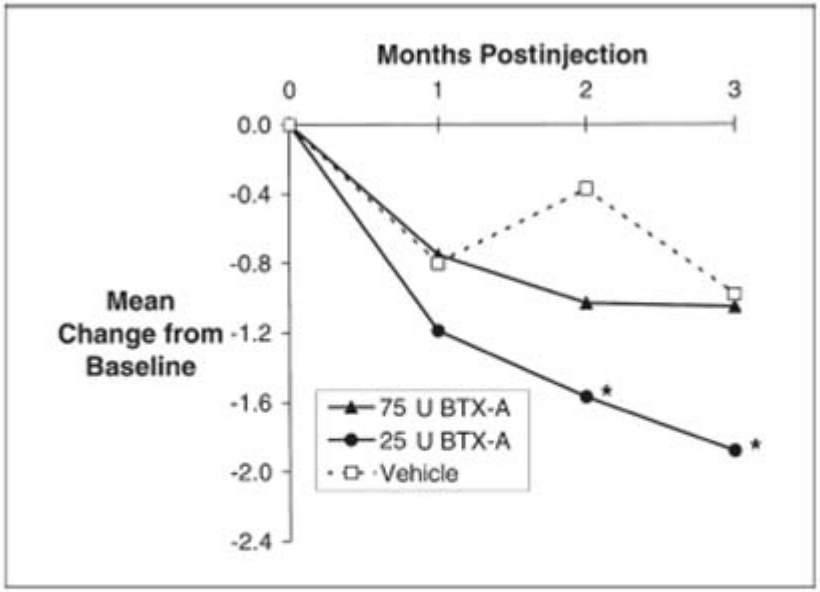


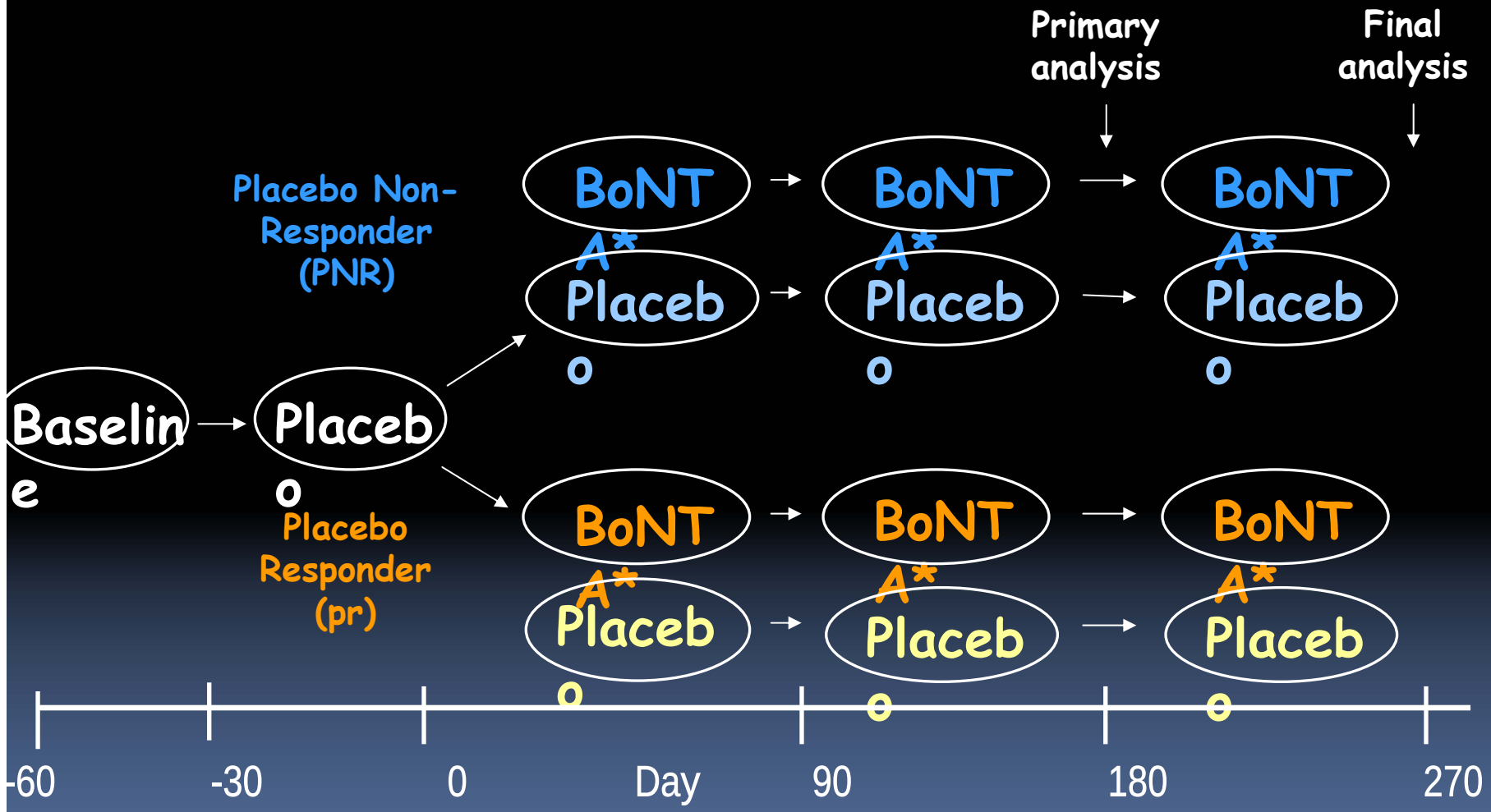
Fig 2.—Mean decrease from baseline in the number of moderate-to-severe migraines per month. Asterisks indicate that the 25-U BTX-A group was significantly different from the vehicle group at 2 and 3 months postinjection ($P \leq .042$).

Clinical data on botulinum toxin in patients with Chronic daily headache

Table 3 Randomized, double-blind, placebo-controlled studies on botulinum toxin in the prophylactic treatment of chronic daily headache

Study	Indication to treatment	Patients, *n*	Results compared with placebo
Ondo *et al.* (2004) [41]	Chronic daily headache	60	No significant reduction but trend (*P* 0.07) in primary endpoint (days with headache)
Silberstein *et al.* (2005) [42•]	Chronic daily headache	702	No significant reduction of headache frequency
Mathew *et al.* (2005) [43•]	Chronic daily headache	355	Primary endpoint (reduction of headache-free days) negative; secondary endpoint (percentage of patients with reduction > 50%) positive
Dodick *et al.* (2005) [44•]	Chronic daily headache	228	Significant reduction of headache frequency in patients not receiving other prophylactic drugs (subanalysis of study [43•])
Elkind and Turkel (2005) [45]	Chronic migraine	355	Significant reduction of migraine frequency for all treatment arms (105–260 U Botox; Allergan, Inc., Irvine, CA, USA) as compared with placebo (subanalysis of study [43•])

2005,Mathew & Silberstein et al. - Study Design

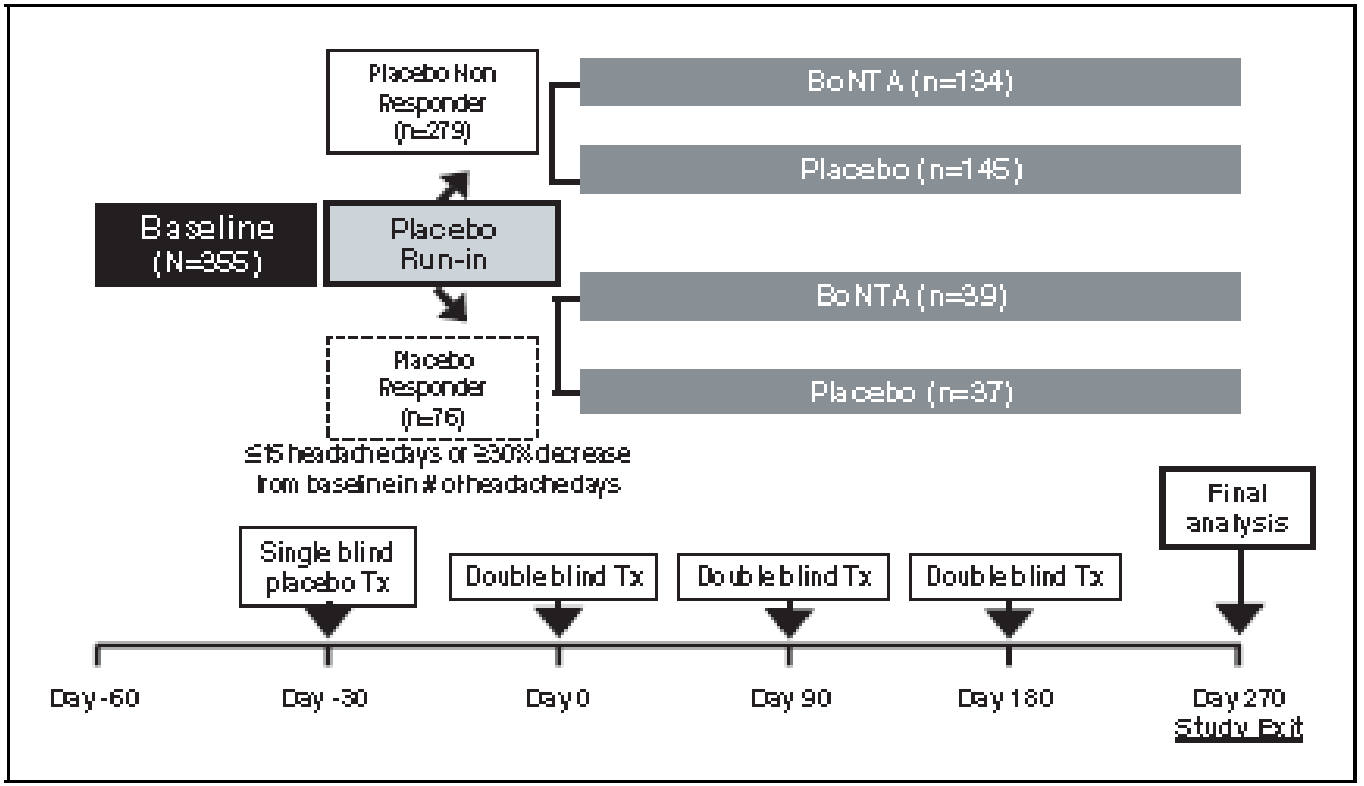


Headache 2005 Apr;45(4):293-307
2005040583

Mathew et al, *Headache* 2005

Research Submission

Botulinum Toxin Type A (BOTOX®) for the Prophylactic Treatment of Chronic Daily Headache: A Randomized, Double-Blind, Placebo-Controlled Trial

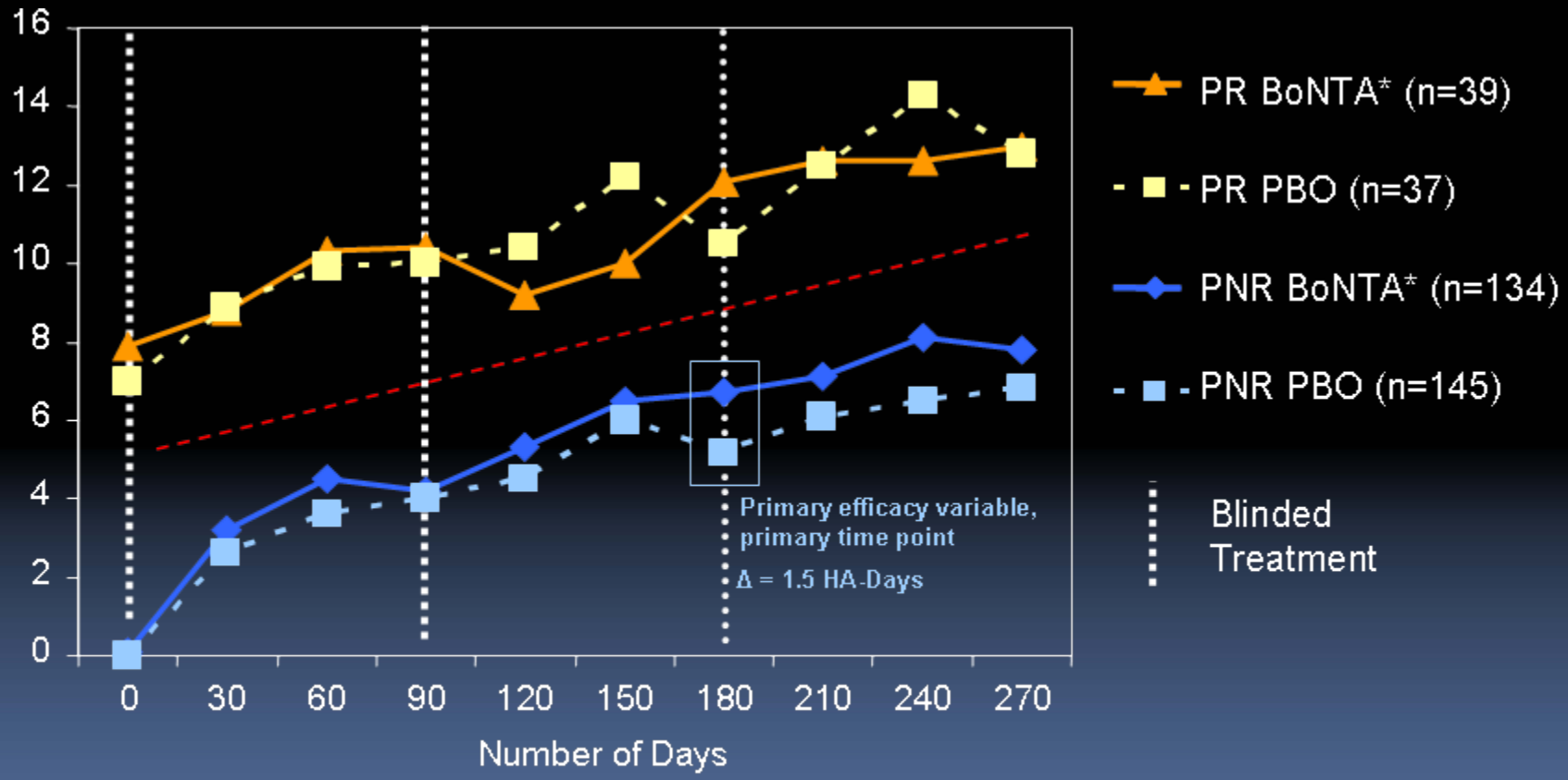


- **Prior medication including prophylactic agents were allowed throughout the study**
  - 36% on prophylactic agents
  - 47% medication overuse

- **Follow-the-pain approach**

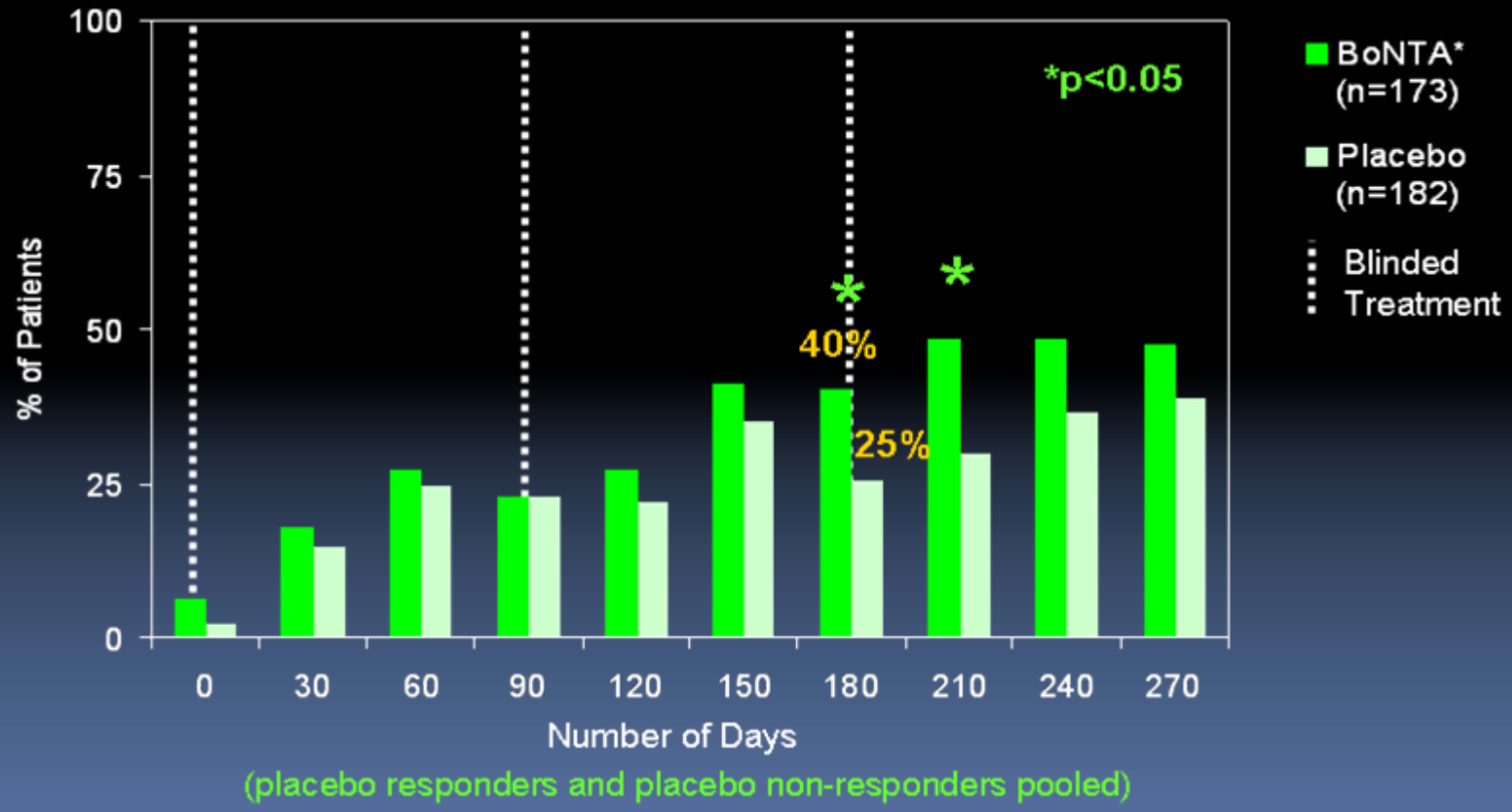
Muscle Injected (Allowable Dose Range)	Treatment Cycle 2 (Day 0)	Treatment Cycle 3 (Day 90)	Treatment Cycle 4 (Day 180)
Frontal/glabellar (25 to 40 U)	38.0 U (40 U)	37.3 U (40 U)	37.1 U (40 U)
Occipitalis (20 U)	19.8 U (20 U)	19.8 U (20 U)	19.7 U (20 U)
Temporalis (20 to 50 U)	42.0 U (40 U)	42.7 U (45 U)	43.7 U (40 U)
Masseter (optional; 0 to 50 U)	8.0 U (0 U)	7.6 U (0 U)	6.5 U (0 U)
Trapezius (20 to 60 U)	47.4 U (60 U)	48.3 U (60 U)	48.4 U (60 U)
Semispinalis (10 to 20 U)	18.2 U (20 U)	18.0 U (20 U)	17.9 U (20 U)
Splenius capitis (10 to 20 U)	18.6 U (20 U)	18.1 U (20 U)	18.1 U (20 U)
Total	190.8 U (200 U)	190.9 U (200 U)	190.5 U (200 U)

Primary efficacy measure- Mean Change in Headache-Free Days

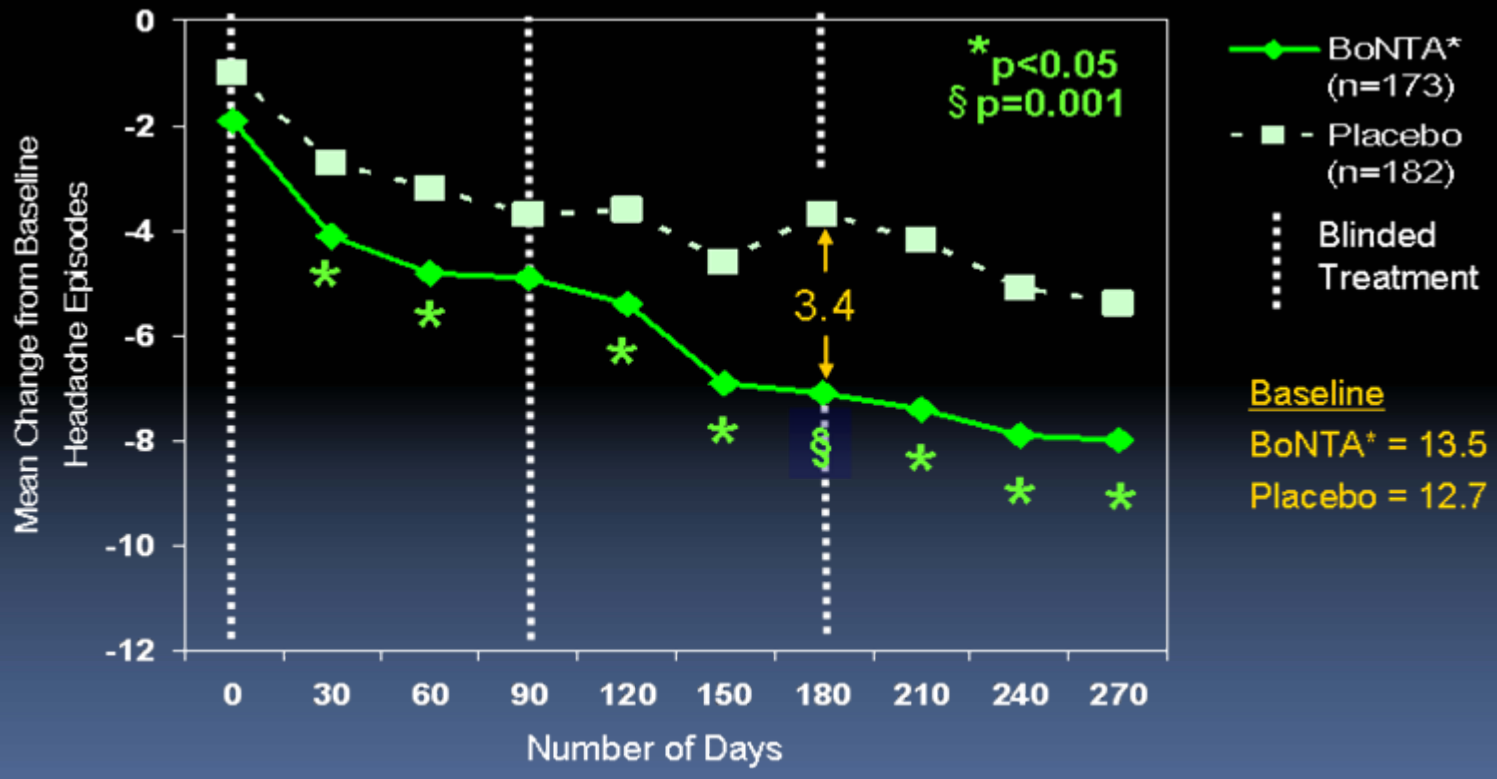


Baseline: PNR BoNTA*= 5.8, PNR Placebo=5.5, pr BoNTA* =10.7, pr Placebo =9.9

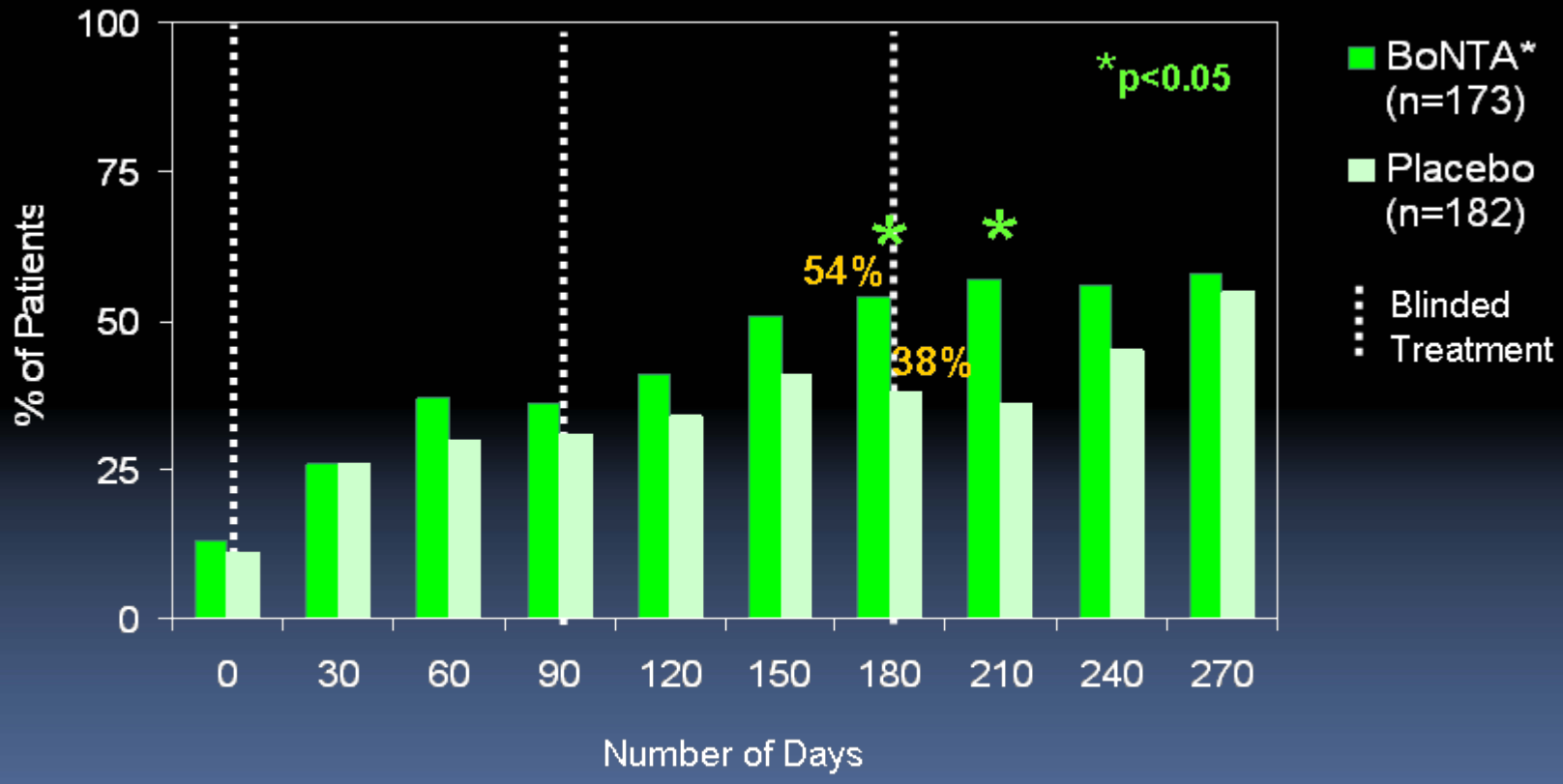
% of Patients with ≥50% Decrease in Headache Days



Mean Change in Frequency of Headache Episodes



% of Patients with ≥50% Decrease in Frequency of Headache Episodes



Adverse Events

Discontinuation due to adverse events: BoNTA* 2.3% and Placebo 0.5%

Treatment-Related Adverse Event	*BoNTA**	*Placebo*	*p-value*
Neck Pain	23 (13.3%)	1 (0.5%)	<0.001
Arm Pain	7 (4%)	1 (0.5%)	0.033
Injection Site Hemorrhage	2 (1.2%)	9 (4.9%)	0.039
Muscular Weakness	38 (22%)	0 (0%)	<0.001
Skin Tightness	8 (4.6%)	0 (0%)	0.003
Blepharoptosis	12 (6.9%)	1 (0.5%)	<0.001

- No significant difference: Headache, neck rigidity, pain, face pain, dysphagia, hypertonia, hyperesthesia, dizziness, pharyngitis, visual disturbance
- Majority of AE's were mild to moderate in severity and transient in nature

Headache 2005 Apr;45(4):315-324
2005040585

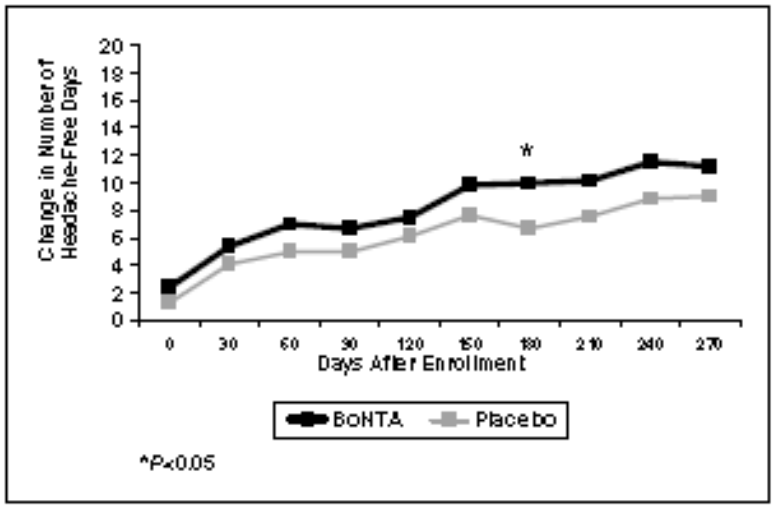
Research Submission

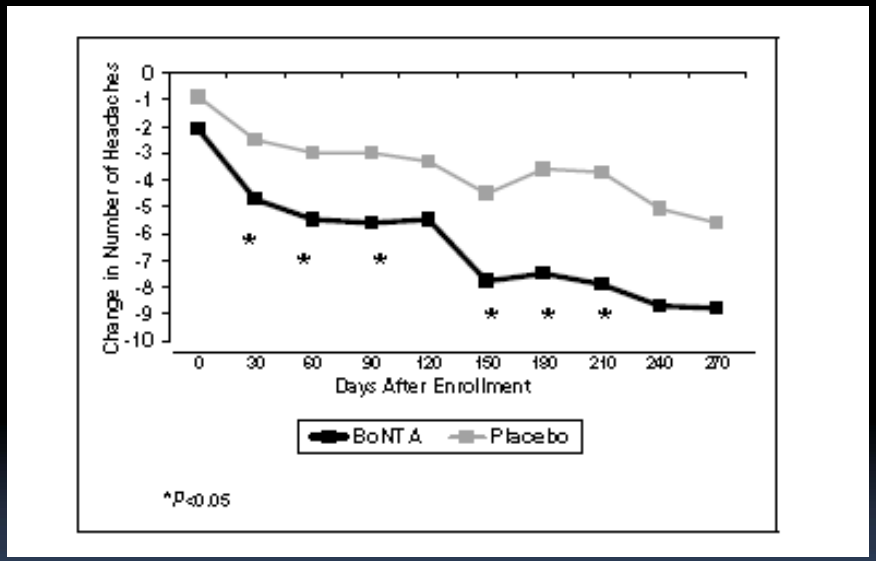
CDH- subgroup Analysis

Botulinum Toxin Type A for the Prophylaxis of Chronic Daily Headache: Subgroup Analysis of Patients Not Receiving Other Prophylactic Medications: A Randomized Double-Blind, Placebo-Controlled Study

- No Concomitant prophylaxis
- Mathew study: 355 patients enrolled
  - 228 (64%) were not taking concurrent prophylactic headache medication at time of enrollment (and during the trial)
- These 228 were pooled patients: both placebo non-responder(PNR) and placebo responder(pr)

Subgroup analysis in those without prophylax



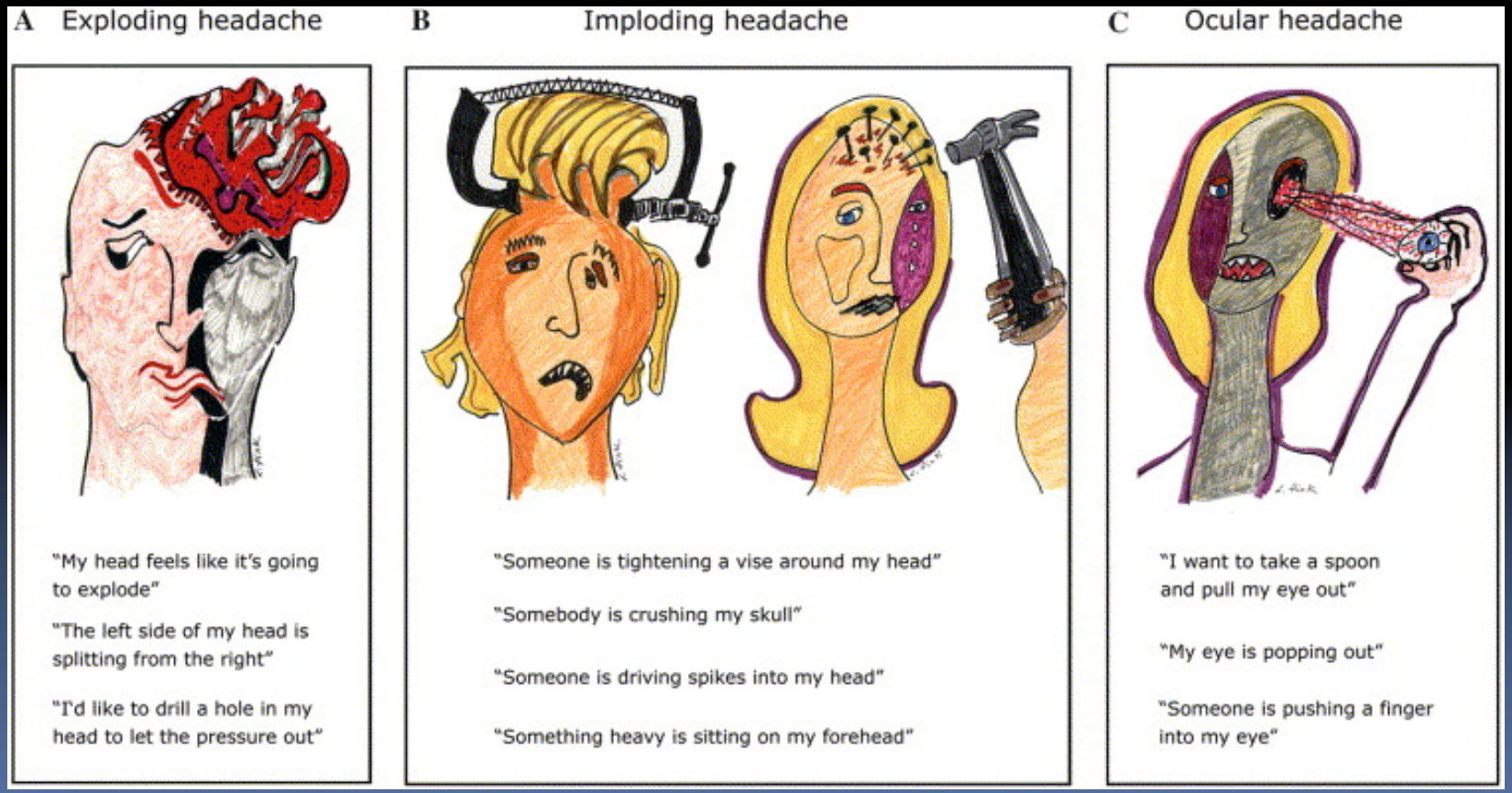


Headache-free days
10.0 vs 6.7 days, p=0.038

Headache frequency ↓

Exploding vs. imploding headache

- Botulinum toxin works only in those with **imploding** and ocular-type headaches but not exploding headaches.



Rami Burstein et al. Pain. 2006 ;125:286-95

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Research Submission

Predictors of Response to Botulinum Toxin Type A (BoNTA) in Chronic Daily Headache

- CM(71) response >> CTTH(11) 76.1% vs 36.4%

CM

- Unilateral
- Pericranial tenderness
- Scalp allodynia

Botulinum Toxin Type A for the Treatment of Headache

Why We Say Yes

Avi Ashkenazi, MD; Stephen Silberstein, MD, FACP

Headache Therapy With Botulinum Toxin

Form Over Substance

Ann Pakalnis, MD; James Couch, MD

Questioning Botulinum Toxin for Headache

Reality or Illusion

E. S. Roach, MD

Arch Neurol 2008 Jan,65,146-152

Possibly related factors so far ..

- Medication overuse (+,poor outcome)
- Disease duration(>30 years, poor outcome)
- Disease severity(headache free days, better)
- Headache characteristics (imploding+, better)
- Outcome measure(difference in headaches of moderate to severe intensity, >4 hrs in duration)
- Treatment related factors

  - Different dosage with different approaches
  - High placebo effect

Arch Neurol 2008 Jan,65,146-152

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY 60th ANNIVERSARY

Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review)

Neurology 2008;70:1707–1714

Table Botulinum neurotoxin (BoNT) for autonomic disorders and pain

Disorder	Class	Outcome measures	Adverse events	Conclusions	Recommendations*	Limitations
Axillary hyperhidrosis	2 Class I	Gravimetry; responder rate; patient satisfaction	No difference between BoNT and placebo	Safe and effective	A	No head-to-head comparisons with other treatment options
Palmar hyperhidrosis	2 Class II	Gravimetry; ninhydrin test; VAS	Injection pain; mild hand muscle weakness	Probably effective	B	No head-to-head comparisons with other treatment options
Gustatory sweating	5 Class III	Area of sweating; ninhydrin test; self assessment	Injection pain	Possibly effective	C	No head-to-head comparisons with other treatment options
Drooling	4 Class II	Drooling scores; weight of dental roles; VAS	Dry mouth	Probably effective	B	No head-to-head comparisons with other treatment options
Detrusor overactivity	2 Class I and 1 Class II	Urodynamic measures; QOL; frequency of incontinence	Urinary retention	Safe and effective	A	No head-to-head comparisons with other treatment options
DSD in spinal cord injury	2 Class II	PRUV	None known	Probably effective	B	No head-to-head comparisons with other treatment options
Low back pain	1 Class II	VAS; Owestry low back pain questionnaire	None known	Possibly effective	C	Diverse etiologies for low back pain
Episodic migraine	2 Class I and 2 Class II	Change in frequency per month; proportion with 50% decease in frequency compared with baseline	Ptosis, local transient pain at the site of injection, bruising, diplopia	Probably ineffective	B	Suboptimal dose and muscle selection may account for treatment failures
Tension-type headache	2 Class I	VAS; area under the curve; proportion of severe headaches post treatment	Transient weakness of neck muscles, local skin tension, ptosis , flulike reaction	Probably ineffective	B	Suboptimal dose and muscle selection may account for treatment failures
Chronic daily headache	4 Class II	Change in headache-free days	Ptosis, transient weakness of neck, flulike reaction	Insufficient evidence	U	Suboptimal dose and muscle selection may account for treatment failures

Chronic migraine clinical trial will be soon published!

GUIDELINES FOR CONTROLLED TRIALS OF PROPHYLACTIC

TREATMENT OF CHRONIC MIGRAINE IN ADULTS

Taskforce of the International Headache Society Clinical Trials Subcommittee

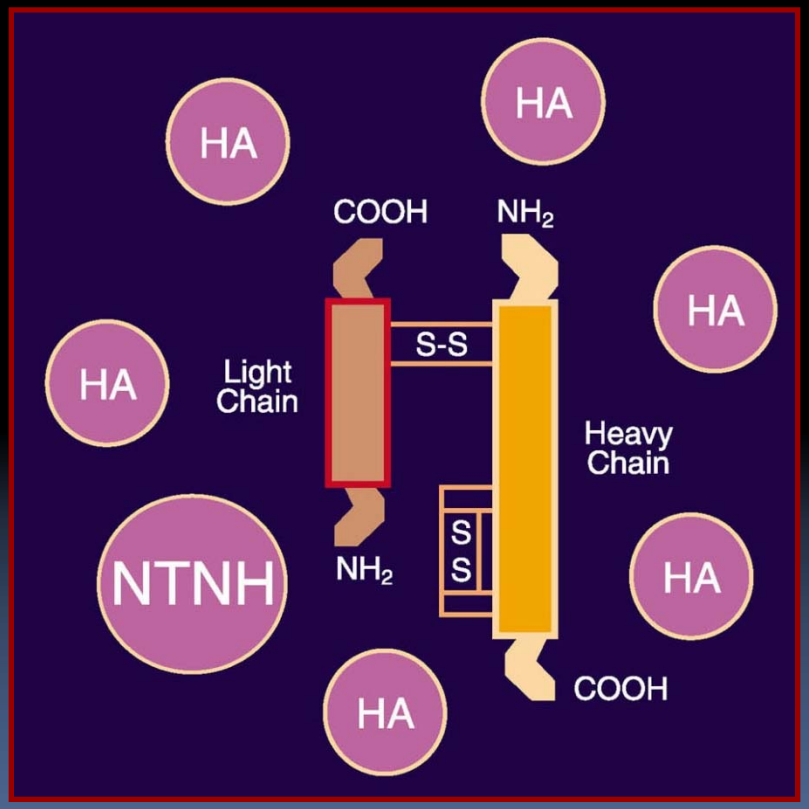
Task force members:

Silberstein S (Chairman)(USA), Tfelt-Hansen P (Co-Chairman) (Denmark), Dodick DW (USA), Limmroth V (Germany), Lipton RB (USA), Pascual J (Spain), Wang SJ (Taiwan)

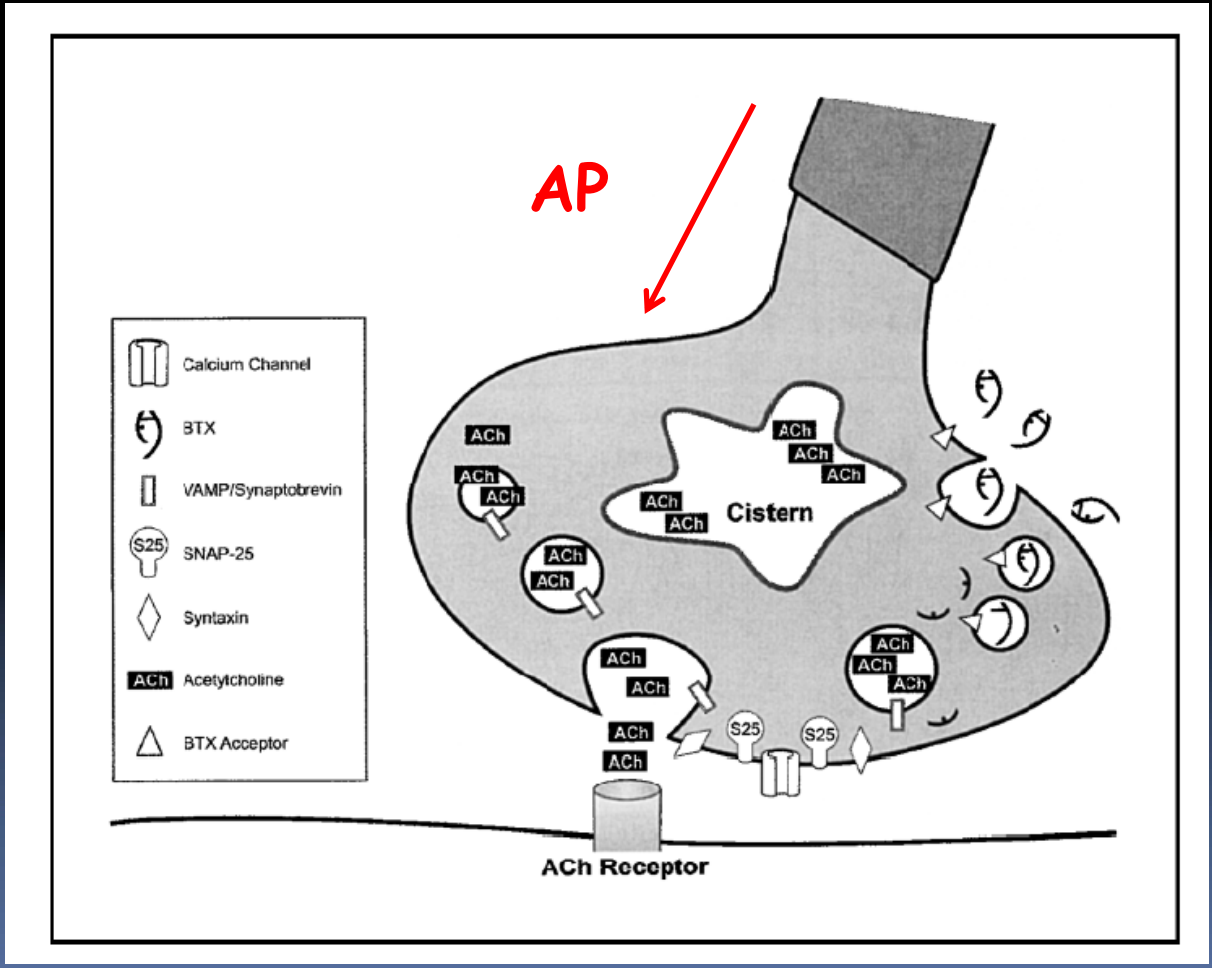
Proposed mechanism of action of BoNT- A in chronic migraine

Botulinum Neurotoxins

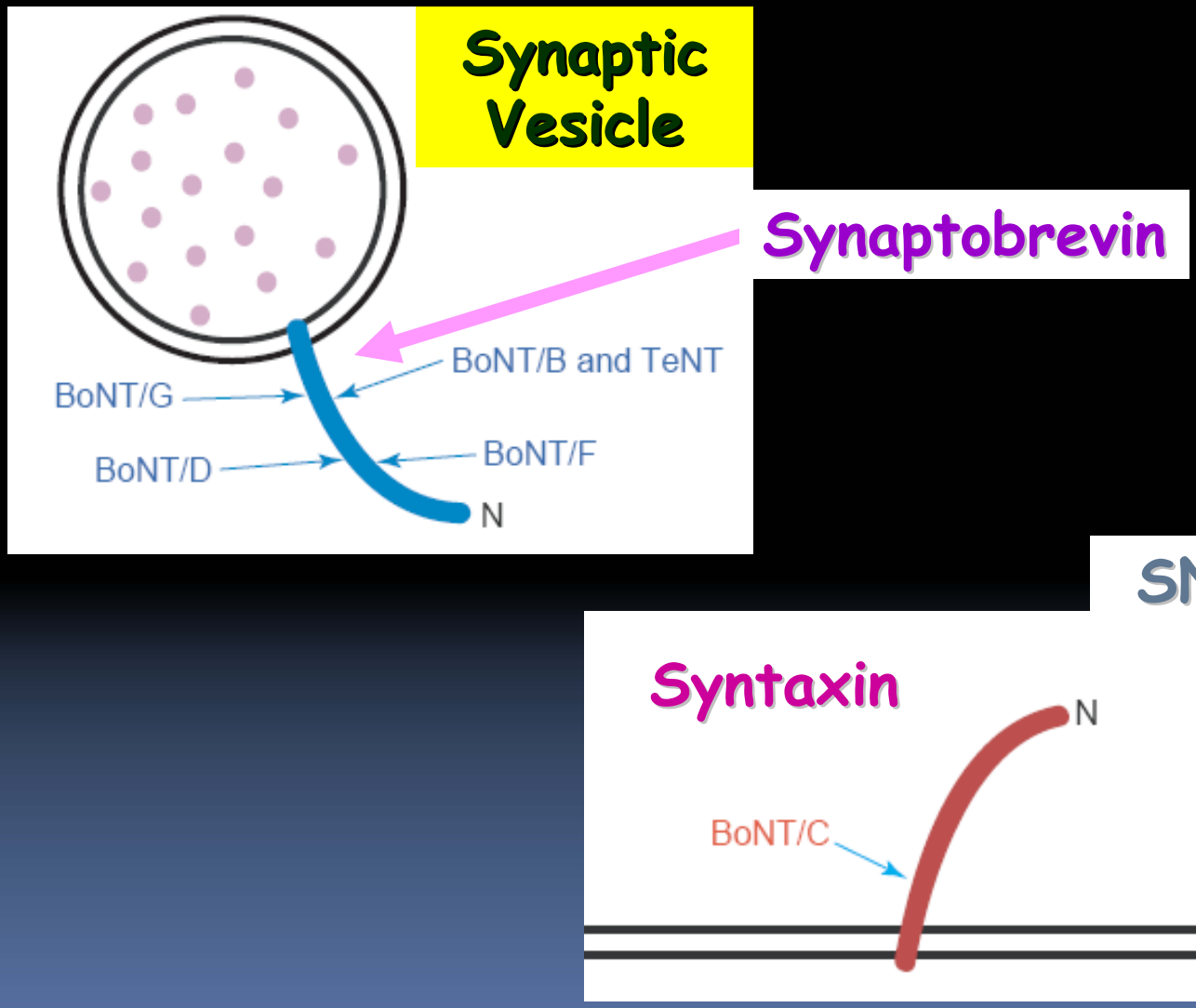
	Neurotoxin Protein Complex Sizes[1]		
A	300 kD	500 kD	900 kD
B	300 kD	500 kD	
C_1	300 kD	500 kD	
D (HA+)	300 kD	500 kD	
E	300 kD		
	300 kD		
G	300 kD		



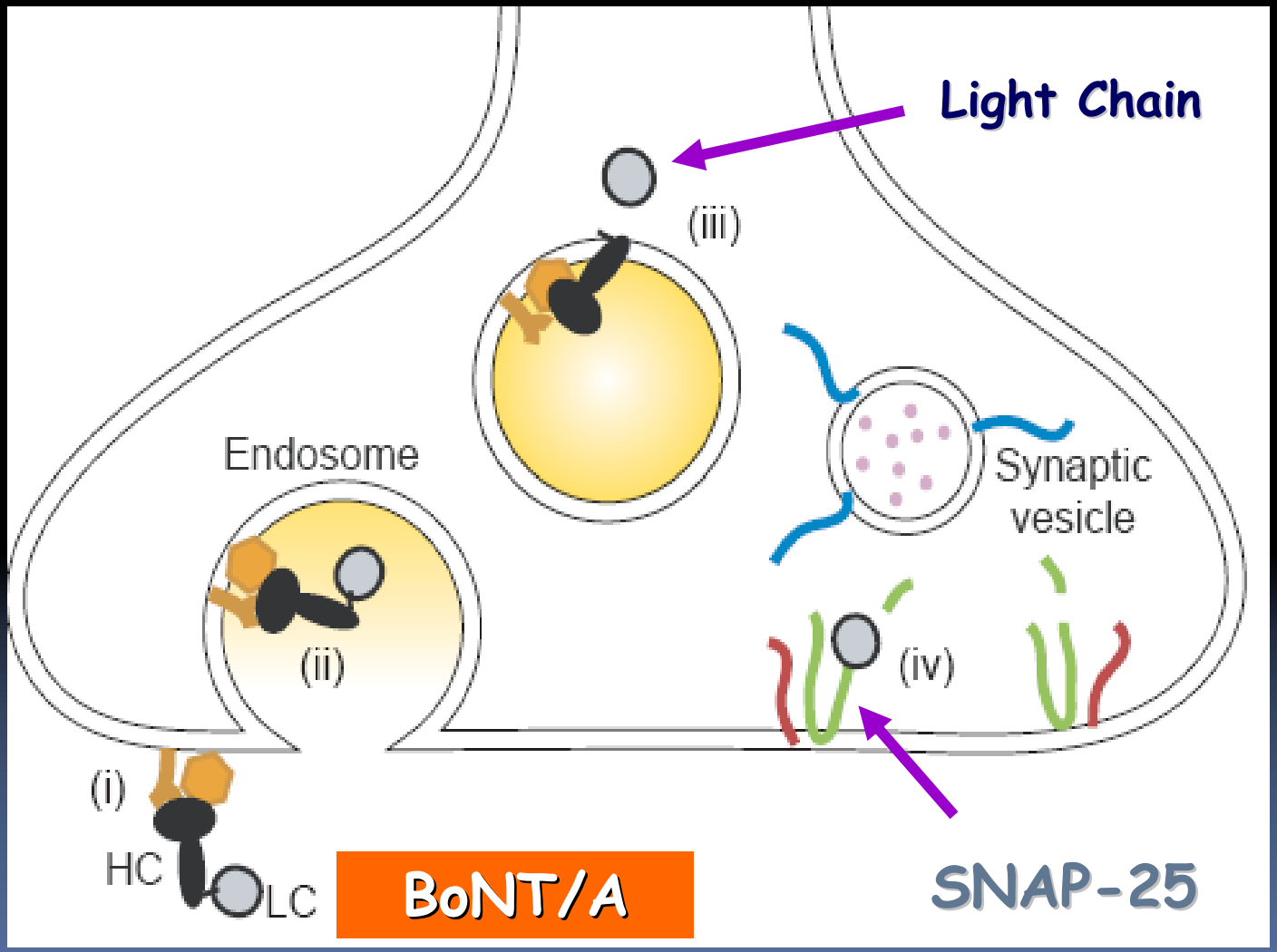
Soluble *N-ethylmaleimide sensitive factor attachment* receptor (SNARE) protein



Cleavage Sites of BoNTs



Adopted from Breidenbach: TRENDS in Molecular Medicine Vol.11 No.8 August


Light Chain
(iii)
Endosome
Synaptic vesicle
(ii)
(iv)
(i)
HC
LC
BoNT/A
SNAP-25

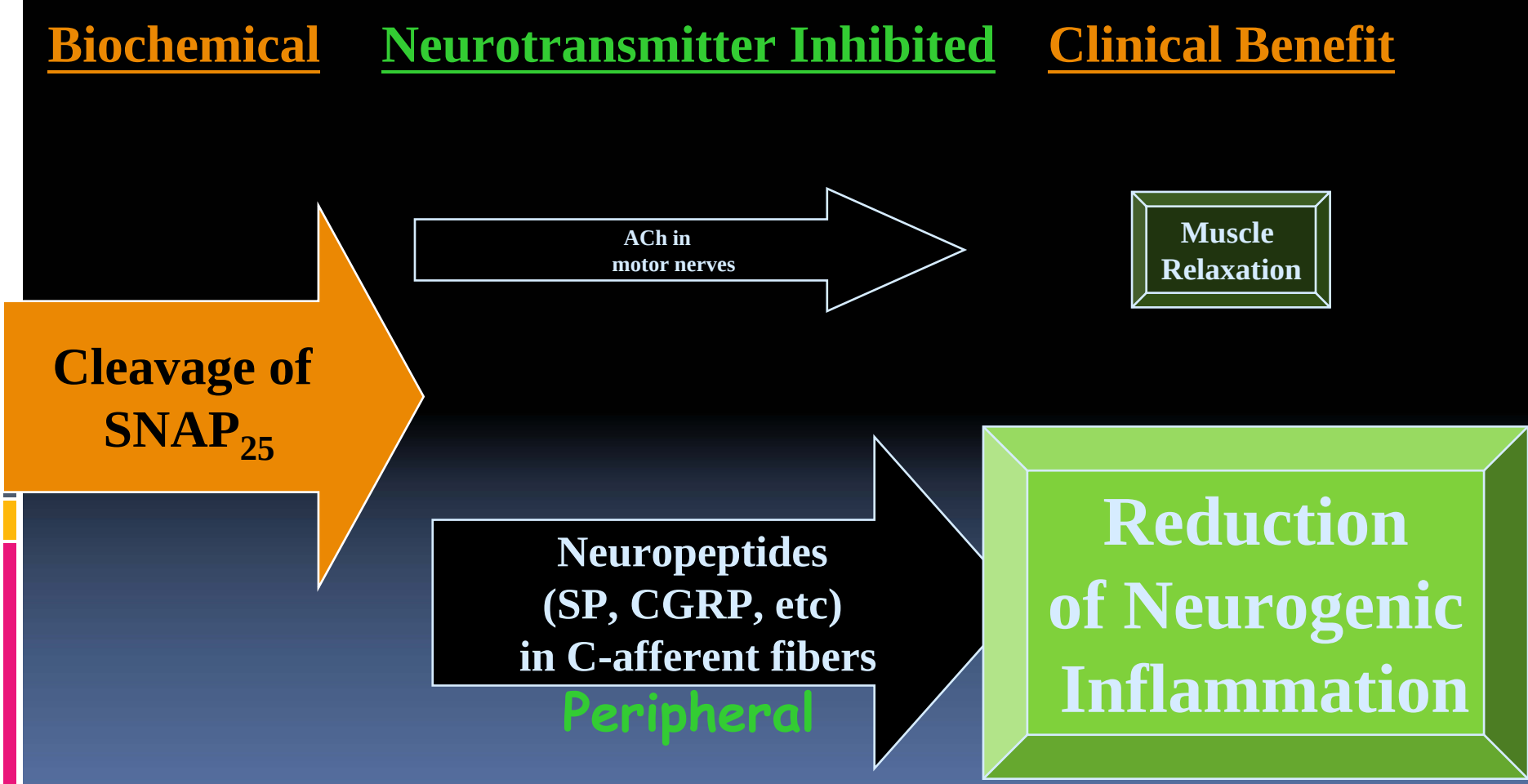
Mechanism of action of BoNT/A in pain/migraine

- Botulinum toxin type A was initially thought to provide pain relief by reducing muscle spasms.
- Even so, the reduction of pain often occurs before the decrease in muscle contractions suggesting that botulinum toxin type A has a more complex mechanism of action than initially hypothesized.
- Current data points to an antinociceptive effect of botulinum toxin type A that is separate from its neuromuscular activity.

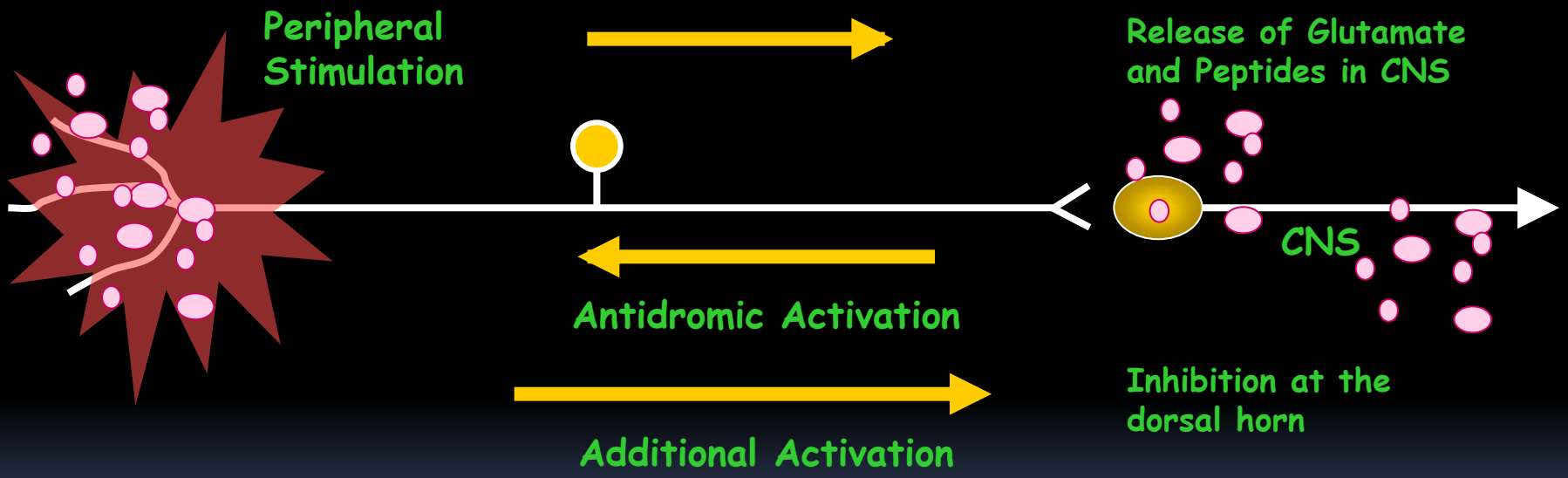
Evidence for Antinociceptive Activity of Botulinum Toxin Type A in Pain Management

- Inhibit substance P release from embryonic dorsal root ganglion neurons in vitro (Welch et al., 2000)
- Inhibit CGRP release from trigeminal ganglion neurons in vitro (Durham and Cady, 2004)
- Inhibit glutamate release from peripheral nociceptors terminating in the dorsal horn in vivo (Cui et al., 2004)
- Reduction of c-fos gene expression in the dorsal horn of the spinal cord, and inhibited the excitation of wide dynamic range neurons of the dorsal horn (Aoki KR et al.,2005).
- In human study of trigeminal-related sensitization, significant suppressive effects of BoNT/A on capsacin induced pain and cutaneous allodynia were reported (Gazerani P et al.,2006,2009).

Reduction of Neurotransmission and Neurogenic Inflammation



Peripheral Sensitization Leads to Central Sensitization



Release of Glutamate and Peptides

Peripheral Sensitization

TRPV1 expression
Increased afferent signals

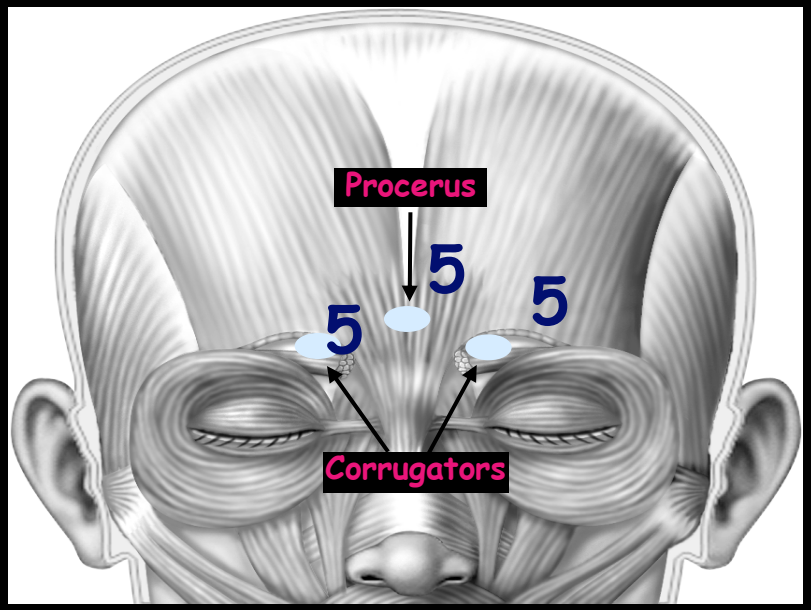
Central Sensitization

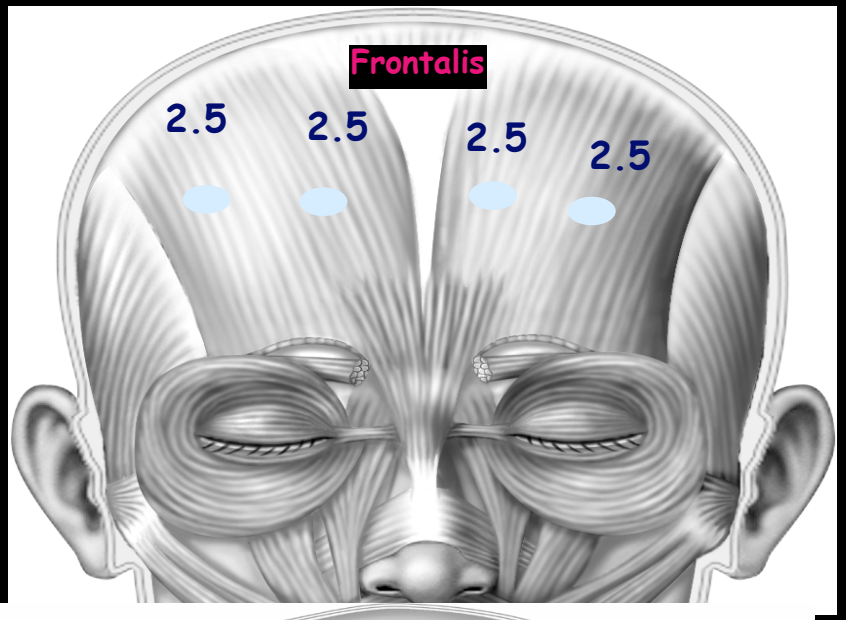
Personal experience

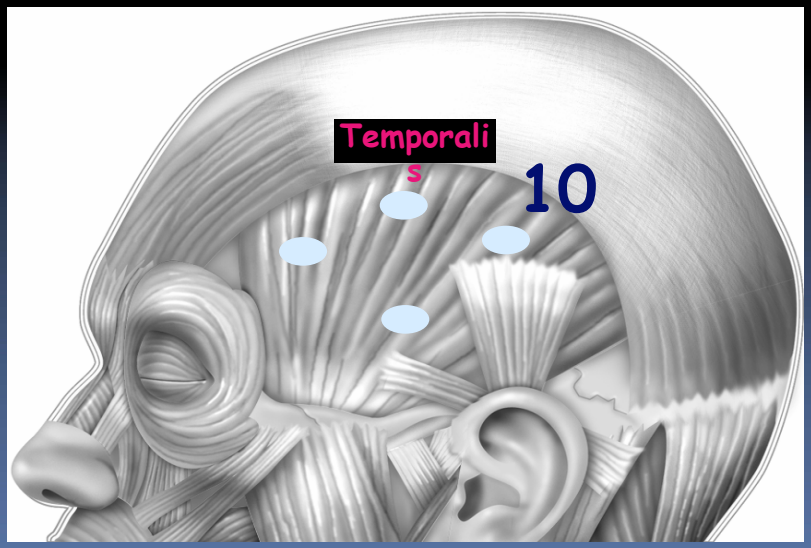
- My injection method is combined follow the pain with fixed side approach with larger dose

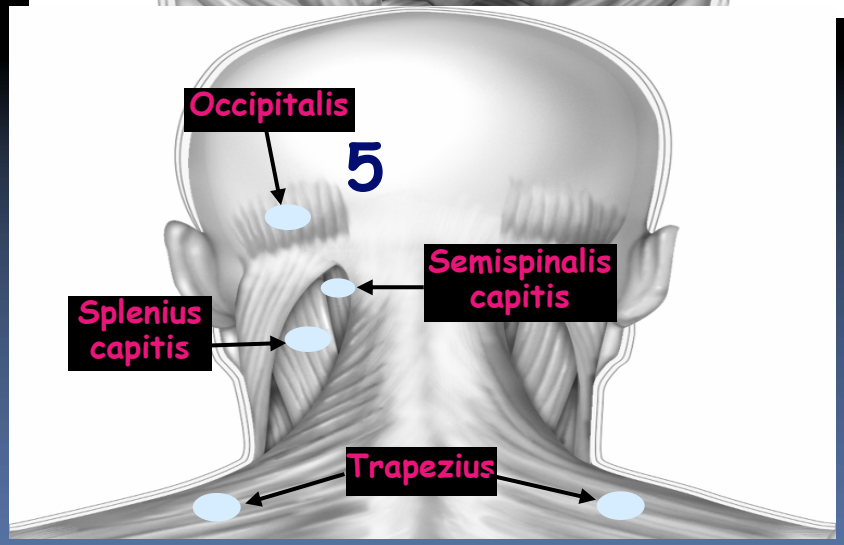
- 9 cases were CM with medical refractory
- 1M/8F
- Mean dose(100-150 units)

Fixed-Site-Fixed-Dose & Follow-the-Pain









Conclusion

適應症

- 眼瞼痙攣
- 半面痙攣
- 局部肌肉痙攣
- 斜視
- 痙攣性斜頸
- 小兒腦性麻痺引起之肌肉痙攣
- 皺眉紋
- 原發性腋窩多汗症
- 成人中風後之手臂痙攣

Off-label use

- 根據衛生署的解釋，藥品「仿單核准適應症外的使用」原則如下：
  一、需基於治療疾病的需要（正當理由）。
  二、需符合醫學原理及臨床藥理（合理使用）。
  三、應據實告知病人。
  四、不得違反藥品使用當時，已知的、具公信力的醫學文獻。
  五、用藥應盡量以單方為主，如同時使用多種藥品，應特別注意其綜合使用的療效、藥品交互作用或不良反應等問題。
- **醫療法**第81條規定：醫療機構診治病人時，應向病人或其法定代理人、配偶、親屬或關係人告知其病情、治療方針、處置、用藥、預後情形及可能之不良反應。

The recommended indications

- Those who demonstrate a lack of improvement from preventive Pharmacotherapy;
- Those who experience severe and intolerable adverse events from preventive medications;
- Those who refuse to use daily medications;

and elderly patients with chronic migraine.


Thank You for your attention