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ACCELERATING THE PACE OF CHANGE
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Cluster Headache and Other TACs

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Disclosures

- Advisory boards of Eli Lilly, Daiichi-Sankyo, Taiwan Pfizer and Taiwan Norvatis.
- Speaker or moderator for Allergan, Pfizer, Eli Lilly, Bayer, and Eisai.

Cluster headache (CH)



- Male preponderance
- 0.1% global population

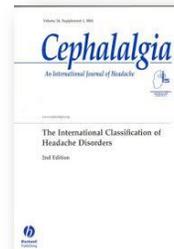


May et al., Nat Rev Dis Primers. 2018

International Classification of Headache Disorders (ICHD-3)

Part I: The Primary Headaches

1. Migraine
2. Tension-type headache
- 3. Trigeminal autonomic cephalalgias (TACs)**
4. Other primary headache disorders



ICHD-3 . Cephalalgia 2018

Trigeminal Autonomic Cephalalgias (TACs)

TACs

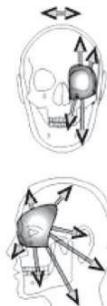
1. Unilateral headache
2. Prominent cranial parasympathetic autonomic features at the same side
 - 3.1 Cluster headache (CH)
 - 3.2 Paroxysmal hemicranias (PH)
 - 3.3 Short-lasting unilateral neuralgiform headache attacks (SUNCT)
 - 3.4 Hemicrania continua (HC)
 - 3.5 Probable trigeminal autonomic cephalalgia



ICHD-3 . Cephalalgia 2018

3.1 Cluster Headache

- A. At least 5 attacks**
- B. Severe or very severe unilateral orbital, supraorbital or temporal pain lasting 15-180 min**
- C. Either or both of the following:**
 1. ≥ 1 ipsilateral symptoms or signs:
 - a) conjunctival injection or lacrimation
 - b) nasal congestion or rhinorrhoea
 - c) eyelid edema
 - d) forehead and facial sweating
 - e) miosis or ptosis
 2. a sense of restlessness or agitation
- D. Frequency from 1/2 d to 8/d for > half the time when active**



ICHD-3 . Cephalalgia 2018

Episodic vs. Chronic CH

3.1.1 Episodic cluster headache

At least 2 **cluster periods** lasting **7 days to 1 year** (when untreated) and separated by pain-free remission periods of **≥3 months**.

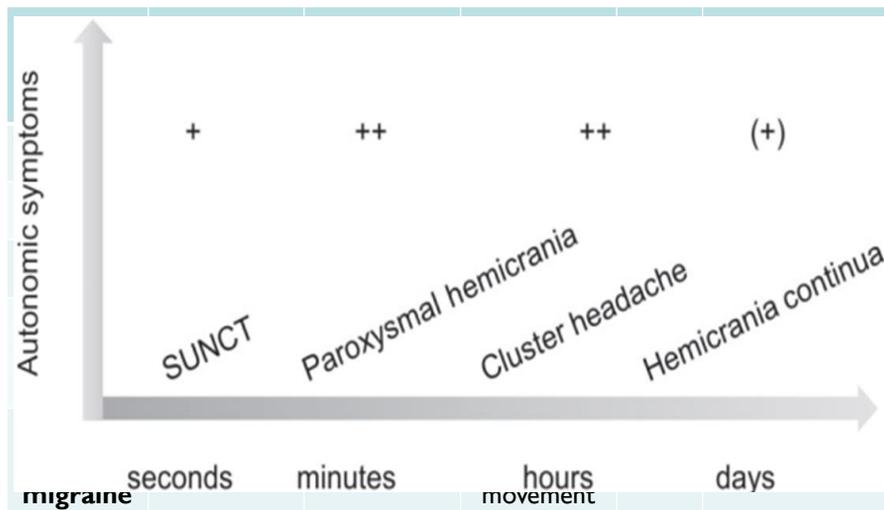
3.1.2 Chronic cluster headache

Occurring without a remission period, or with remissions lasting **<3 months**, for at least 1 year.



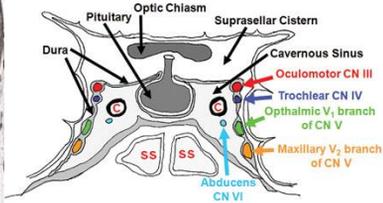
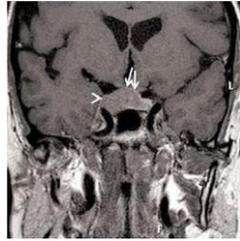
ICHD-3 . Cephalalgia 2018

Differential Diagnosis



Modified from May et al., Nat Rev Dis Primers. 2018

Should Patients with TACs Receive Image Studies?



- TACs can be secondary to **structural lesions**
- Both intra/extra cranial neurovascular and structural lesions, esp. **pituitary, carotid or cavernous sinus lesion**
- **Additional imaging** for assessing intracranial and cervical vasculature, the sellar and paranasal regions

Francis.J Headache Pain Manag. 2017

Epidemiology

Prevalence of Cluster Headache

- **In Westerns:** the prevalence is estimated as
 - 0.01% ~ 0.4% in the general population¹⁻⁷
 - 8% ~ 10% in a headache clinic population⁸
- **In Asians:** no published data
 - 0.03% (1/3377) (unpublished, Wang SJ, Taipei, 1997)

1. Ekbom et al. *Headache*, 1978; 2. D'Alessandro et al. *Cephalalgia*, 1986;

3. Tonon et al. *Neurology*, 2002; 4. Evers et al. *JNNP*, 2007; 5. Takele et al. *J Headache Pain*, 2008;

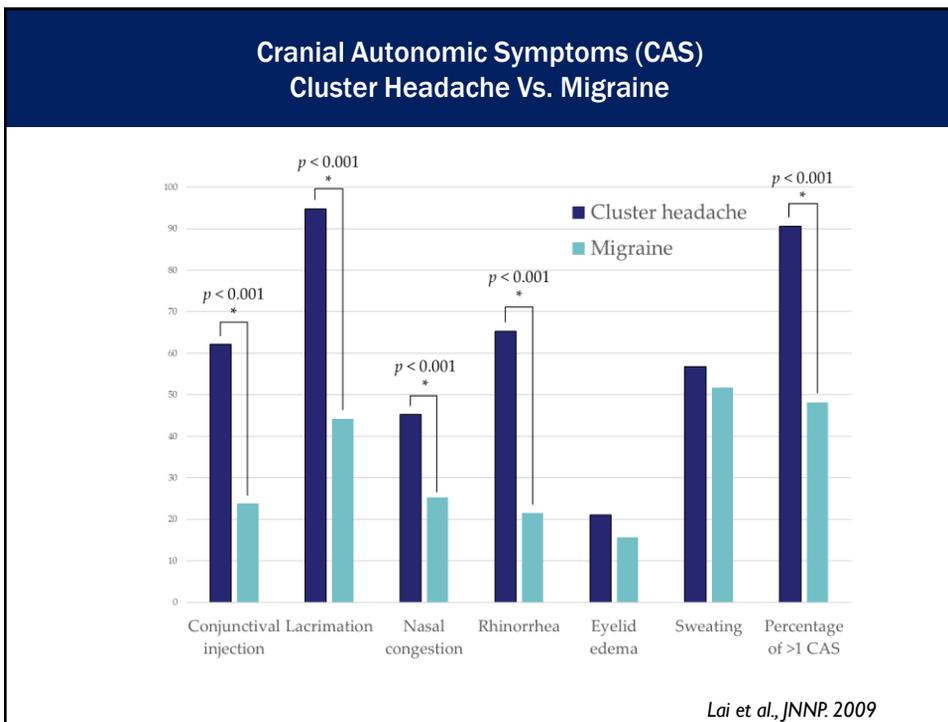
6. Shahbeigi et al. *Neurol Sci*, 2012; 7. Sjaastad and Bakketeig. *Cephalalgia*, 2003;

8. Manzoni et al. *Cephalalgia*, 1991

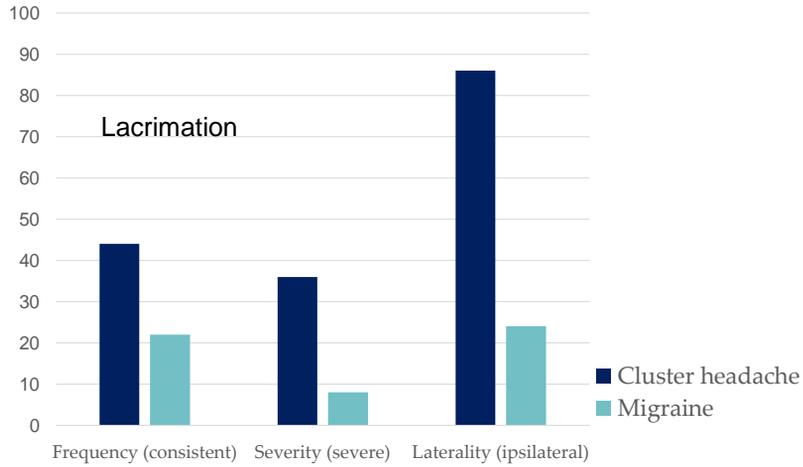
	Asian Studies (Taiwan, Japan, China, India, Korea)	Western Studies (UK, USA)
Numbers	540	1364
M:F Ratio	6.2: 1	2.6: 1
CCH (%)	2.4%	21%
Mean age at onset (yrs)	30.6	29.0
Family history of CH	2.4%	15.7%
Predominant laterality	Right	Right
Most cranial autonomic features	Lacrimation (78.8%)	Lacrimation (91%)
Sense of agitation or restlessness	49.8%	98.2%
Aura	<1%	19.8%
Most common time	Nocturnal, afternoon	Nocturnal
Seasonal propensity	Dec., Mar (Spring)	Spring and Autumn

Lin et al., *Cephalalgia*. 2003; Imai et al., *Cephalalgia*. 2010; Dong et al., *J Headache and Pain*. 2013; Bahra et al., *Neurology*. 2002; Bhargava et al., *J Neurosci Rural Pract*. 2014; Moon et al., *J Korean Med Sci* 2017; Rozen and Fishman. *Headache*. 2012

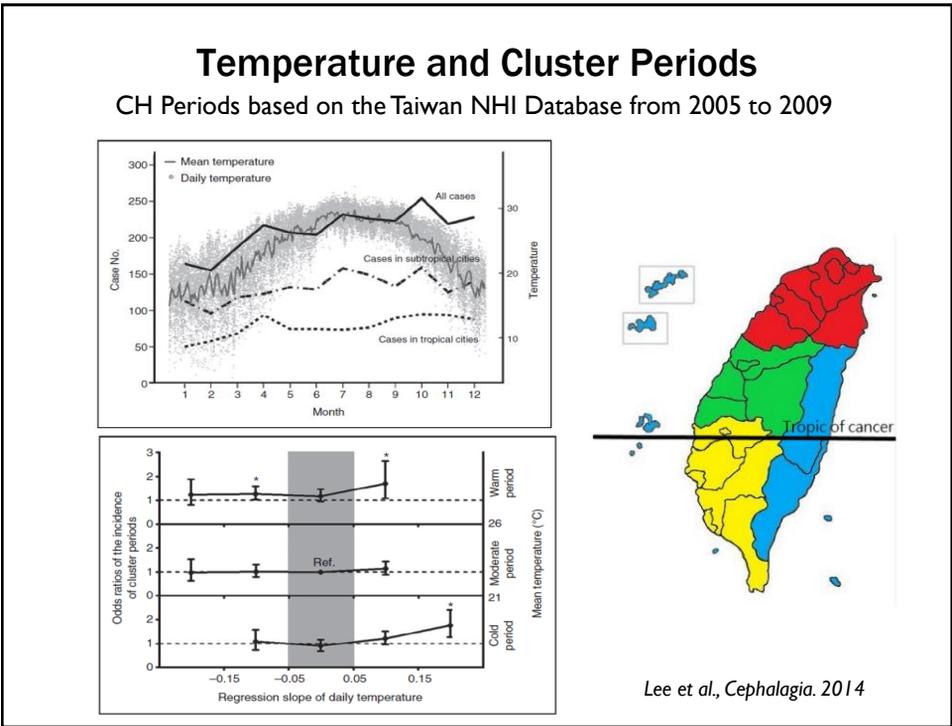
	Taiwan 2003	Japan 2010	China 2013	India 2014	Korea 2017	UK 2002
Numbers	104	86	120	30	200	230
M:F Ratio	6.4: 1	3.8: 1	7:1	9:1	7:1	2.5: 1
CCH (%)	0	3.5%	7.5%	0	0.5%	21%
Mean age at onset	26.9	31.0	26.7	38	30.7	28.4
Family history	5.8%	--	6.7%	0	--	5.0%
Predominant laterality	Right	Right	Right	Right	Left	Right
Most cranial autonomic features	Lacrimation (83%)	Lacrimation (66.3%)	Lacrimation (72.5%)	Lacrimation (83.3%)	Lacrimation (85.5%)	Lacrimation (91%)
Most additional features	Phonophobia (58%)	Nausea (39.5%)	Nausea (60%)	Phonophobia (40%)	Nausea (48.6%)	Phonophobia (56%)
Sense of agitation or restlessness	51%	68.9%	38.3%	80%	43.5%	93%
Aura	1%	--	0	0	0.5%	14%
Most common time	Midnight (28%)	Nocturnally (47.7%)	7am - 10am, 2pm - 4pm	2pm - 5pm, 12am - 4pm	Night (66.4%)	Nocturnally (73%)



CAS in cluster headache vs. migraine

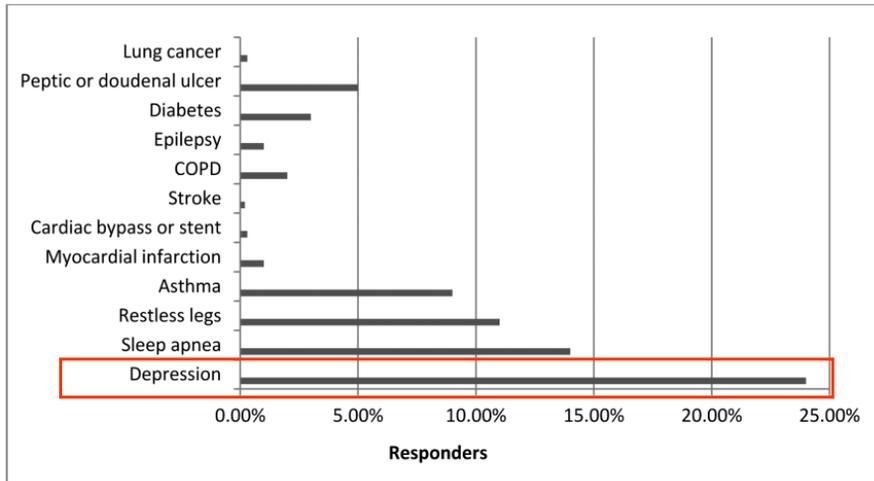


Lai et al., JNNP. 2009



Lee et al., Cephalgia. 2014

Comorbidities in patients with CH

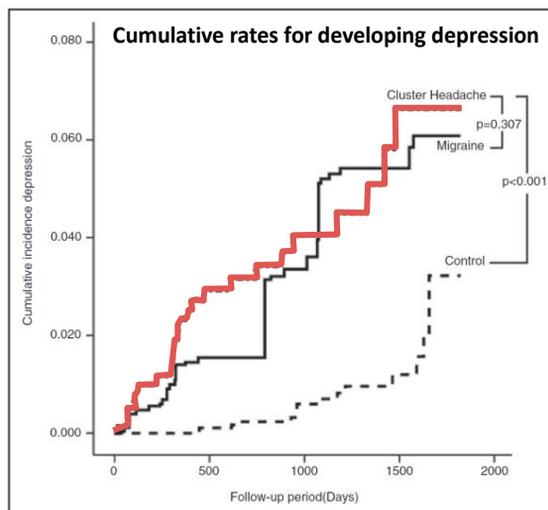


N=1134 : 816 M (72%)/318 F (28%).

Rozen and Fishman. Headache. 2012

CH and Depression in Taiwan (Claims Data)

- Female CH patients have a greater risk.
- 3.6% patients developed depression (median 2.5 yr)
- CH vs. control: HR=5.6
- CH vs: migraine HR=1.1
- Risk factor: Number of cluster period/ year



Liang et al., Cephalgia. 2012

Genetics (I)

- CH in monozygotic twins → suggested a genetic component
- **CH** in the first degree relatives: **14-45** fold risks
Migraine in first degree relatives: 2-8 fold risks

Table 2. Age and gender standardised risk of cluster headache in relatives of patients

Country	Affected relatives	Number of affected relatives <i>Observed</i>	<i>Expected</i>	Population relative risk (95% CI)
Denmark ²⁷	First-degree	26	5.40	4.7 (3.1–6.9)
	Second-degree	10	13.20	0.8 (0.4–1.4)
USA ²⁸	First-degree	41	2.70	15.2 (11.1–21.1)*
Italy ²⁹	First-degree	39	2.97	13.1 (9.0–17.3)
	Second-degree	18	6.69	2.7 (1.5–3.9)
France ³⁰	First-degree	22	1.25	17.6 (10.2–24.9)*

Prevalence of cluster headache is assumed to be one person per 500. *Calculation made without correction for age.

Taga et al., *Neurol Sci.* 2015

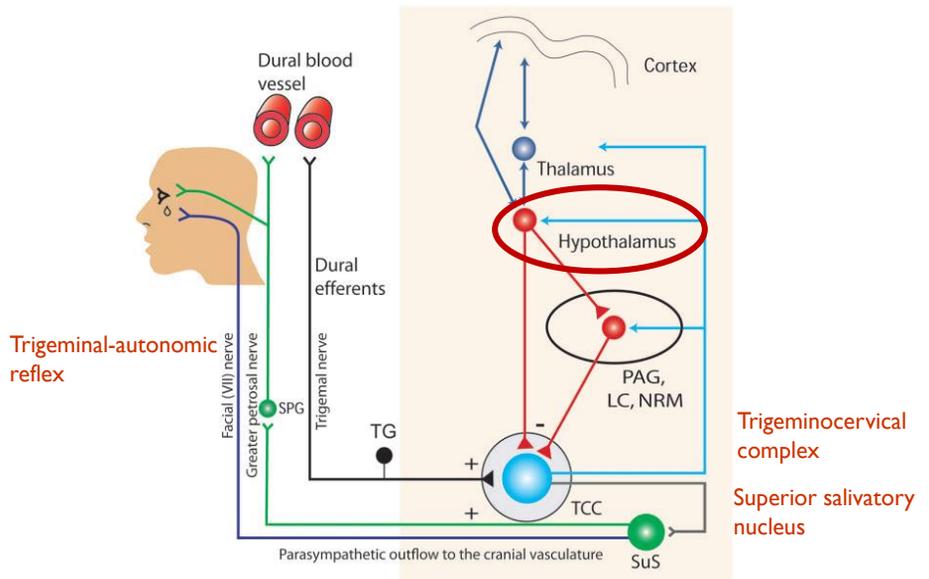
Cruz et al., *Arq Neuropsiquiatr.* 2013

Genetics (II)

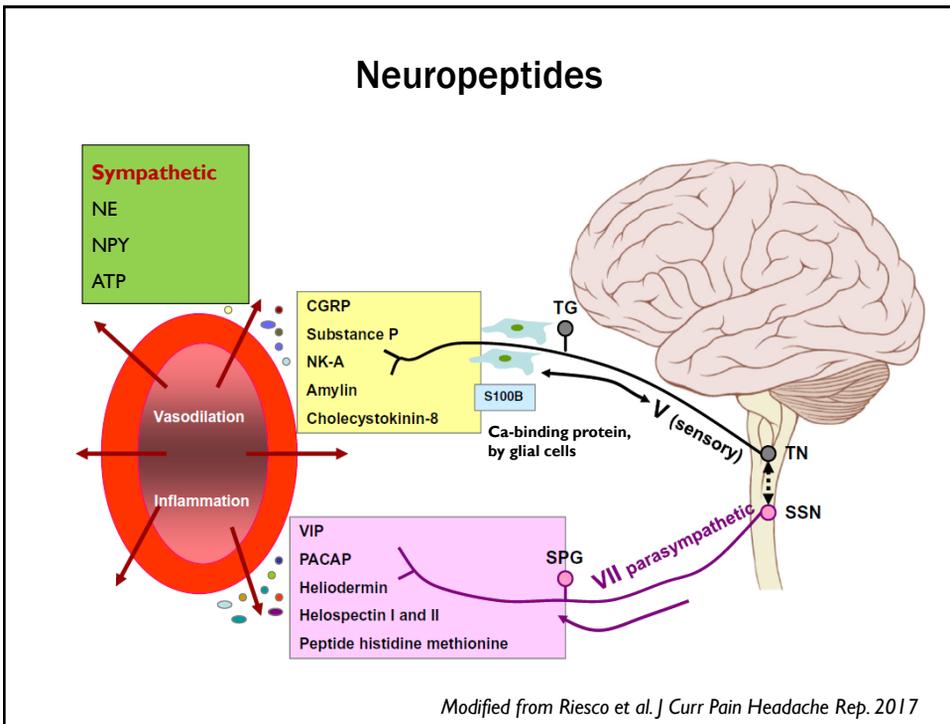
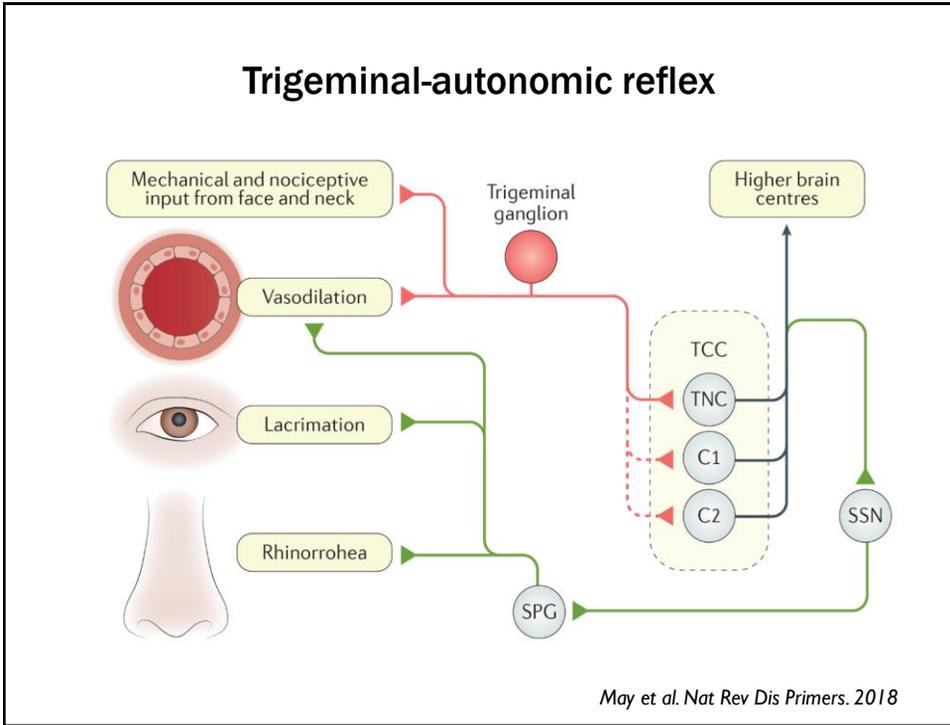
Study	Authors	Study	Authors		
HCRT2 (1246 G>A, rs2653349, rs5443)	Rainero, 2004	Mitochondrial DNA mutation	Cortelli, 1995		
	Bartsch, 2004		NOS (NOS1, NOS2A, NOS3)		
	Schürks, 2006			Sjostrand, 2002	
	Baumber, 2006			CACNA1A	
	Weller, 2015				Sjostrand, 2001
	Katsarou, 2018				CLOCK (3111T>C, rs1801260)
Fan, 2018	Rainero, 2005				
Fourier, 2019	Cevoli, 2008				
ADH4 (rs1800759, rs1126671)	Rainero, 2010	Zarrilli, 2015			
	Zarrilli, 2015	Fan, 2018			
	Fourier, 2016	Fourier, 2019			
	Fan, 2018	PER3			
	Ofte, 2016				
		GWAS (ADCYAP1R1, MME)	Bacchelli, 2016		
			Ran, 2017		

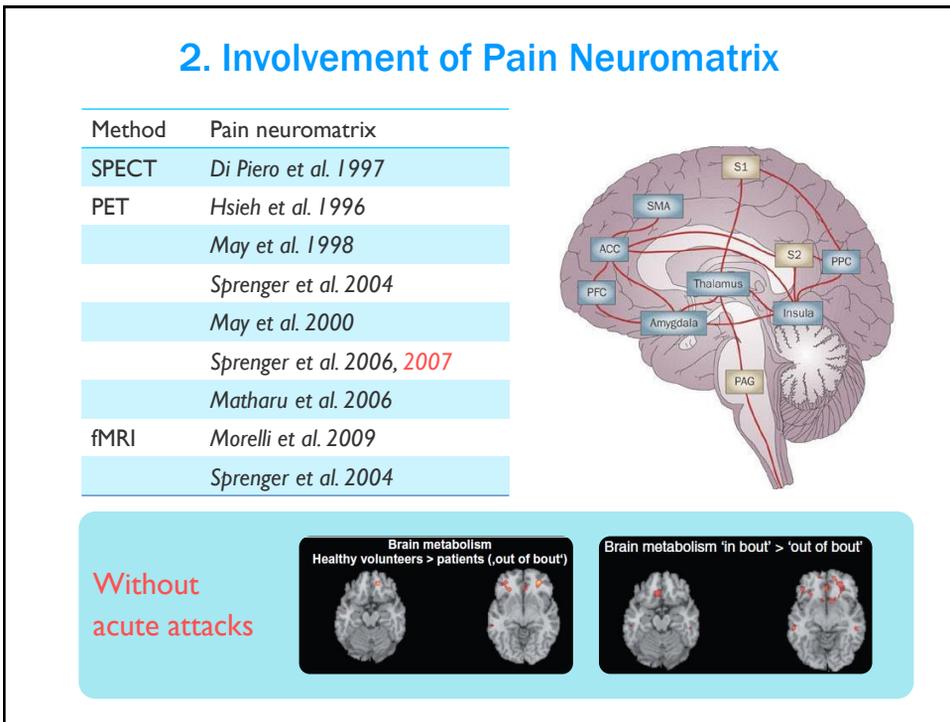
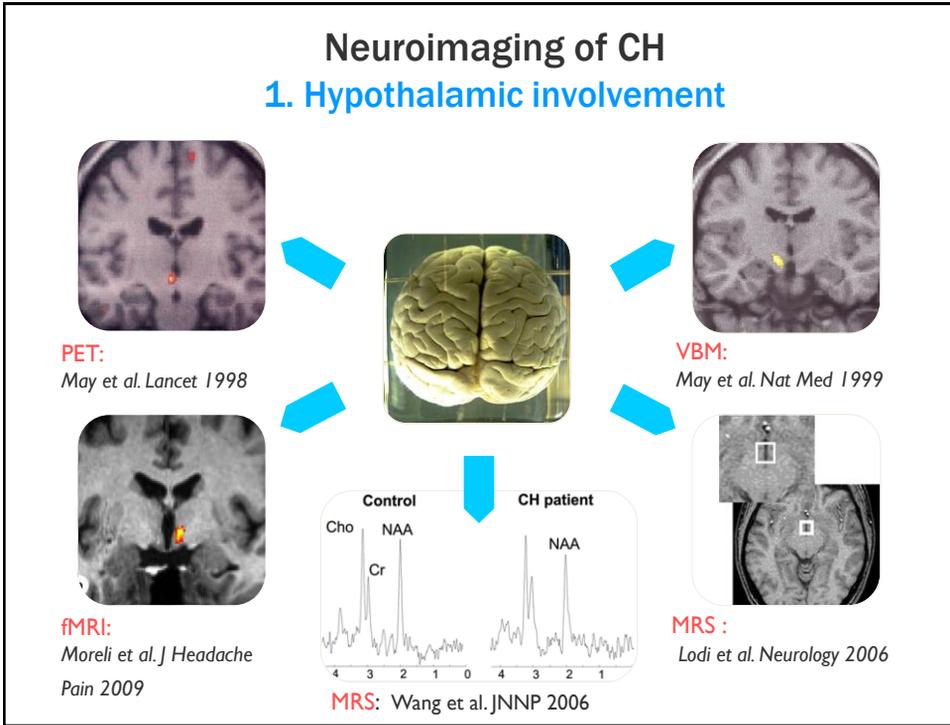
Pathophysiology

Pathophysiology of TACs

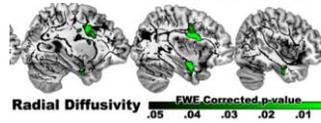
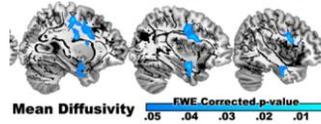
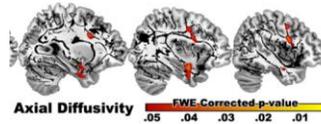
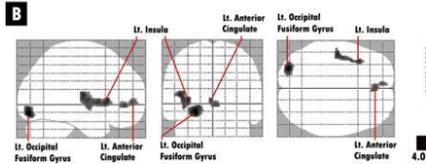
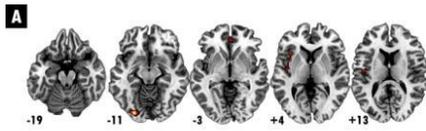


Akerman et al. Brain. 2012





Dynamic structural changes **between bout periods**



- in-bout CH / out-of-bout CH :

ACC, insula, fusiform gyrus

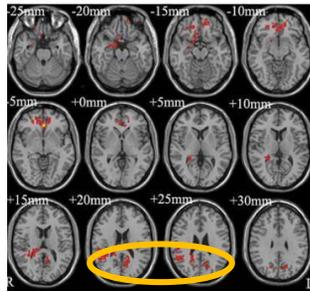
Yang et al. Pain 2013

- in-bout CH / out-of-bout CH :

cerebellar WM areas

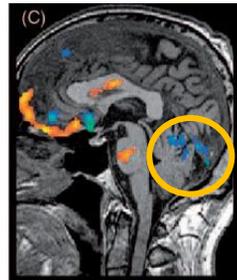
Chou et al. Cephalgia 2014

3. Involvement of Other Networks



- Seed-based rsfMRI: hypothalamus
- in attack vs. out of attack : pain network and **occipital lobe**

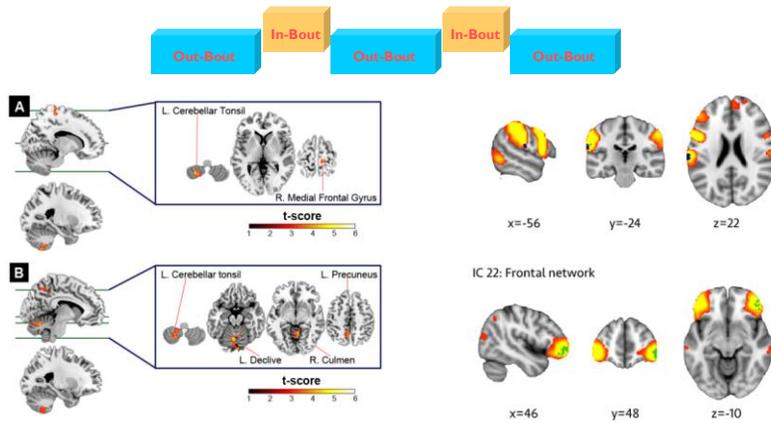
Qiu et al. PLoS One. 2013



- fMRI: a chronic CH
- Pain vs. pain-free (Tx): hypothalamus, pain matrix and **cerebellum**

Morelli et al. Cephalgia 2013

Dynamic functional changes **between bout periods**

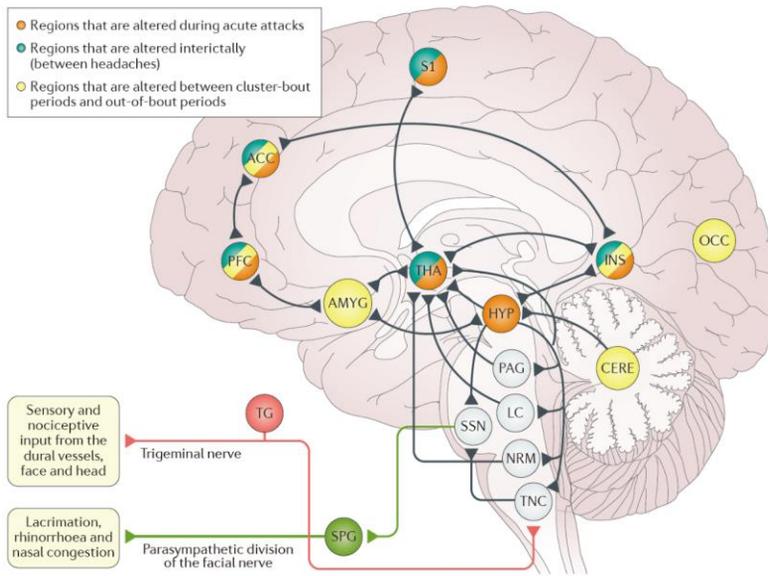


- in-bout CH / out-of-bout CH : **cerebellum, frontal and occipital areas**
- in-bout CH / out-of-bout CH : **frontal and dorsal attention networks**

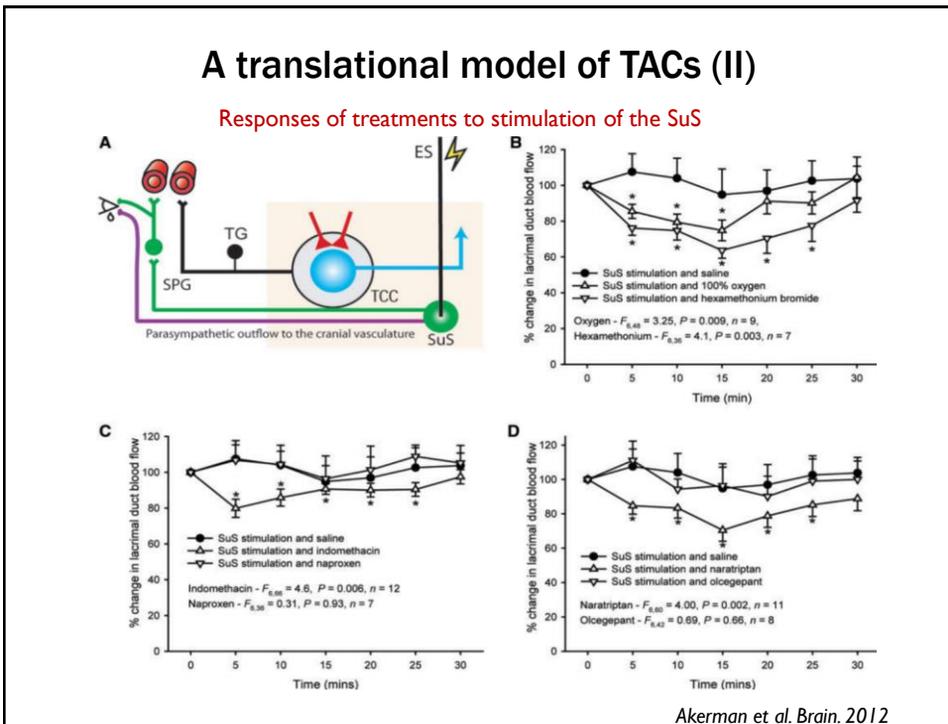
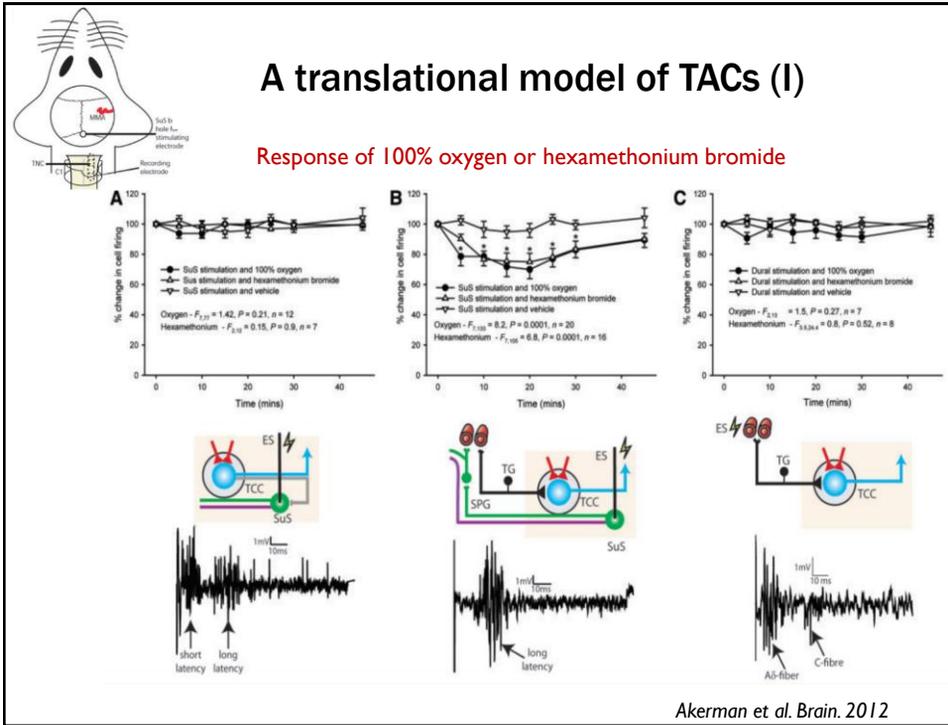
Yang et al. *J. Neurol. Neurosurg. Psychiatry*. 2015

Chou et al. *Cephalalgia* 2017

An Integrative View of CH



May et al. *Nat Rev Dis Primers*. 2018



Management

Acute Abortive Treatment of CH

- **Level A:** *should be offered*
 - Sumatriptan 6 mg s.c.
 - Sumatriptan 20 mg nasal spray
 - Zolmitriptan 5-10 mg nasal spray
 - 100% oxygen 7-10 L/min (15min)
- **Level B:** *should be considered*
 - Octreotide 100 ug s.c.
 - Lidocaine 1ml (4-10%) nasal spray



Holton. Mayo Clin Proc 1956

Robbins et al., Headache. 2016

Ramusino et al., J Oral Facial Pain Headache. 2019

Oxygen Treatment of Acute CH

- **Low-flow oxygen (6–7 l/min):**
efficacy in **56%-82%** of attacks.
- **High-flow oxygen (12 l/min):**
efficacy in **78%** of attacks.
- **Hyperbaric oxygen therapy:**
evidence only for an acute (**50-100%**) in a few small studies
but not prophylaxis.

Petersen et al. Cephalagia 2014; Rozan et al., Pain Med 2013

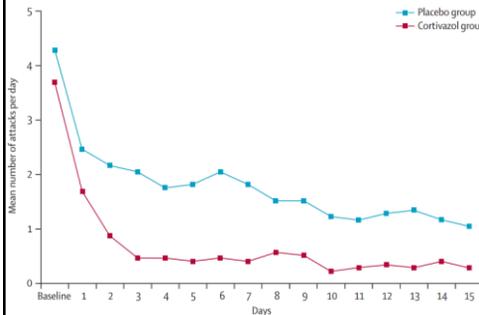
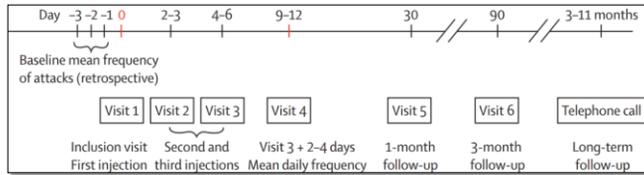
Cohen et al JAMA. 2009; Nilsson Remahl et al., Cephalagia 2002

Transitional Treatment of CH

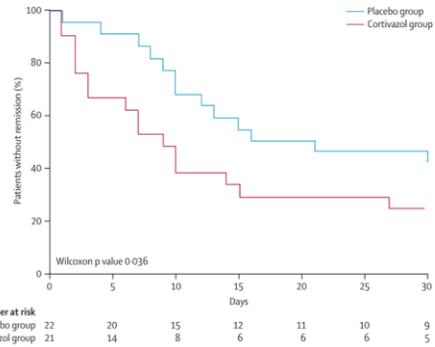
- **Corticosteroids:**
 - prednisone (1 mg/kg, 60-100 mg/day), 5-7 days, with tapering off the dosage by 10 mg every 2-3 days
- **Ergotamine:**
 - 1-2 mg/day, during a short course (<6 weeks)
- **Dihydroergotamine:**
 - intramuscular injections (1 mg once or twice daily) for 1 week
 - intravenous infusion of 1 to 2 mg/d for 3 days
- **Occipital nerve blockade:**
 - a mixture injection of lidocaine and corticosteroids
once every night to 12 weeks (80% improved, hair loss, skin atrophy)

May et al. Nat Rev Dis Primers. 2018

Suboccipital steroid injections for CH



Mean number of attacks during days 1-15



Kaplan-Meier curves of remission before day 30

Leroux et al. Lancet Neurol. 2011

Preventive Treatment of CH

	EFNS evidence	AAN evidence	Dose per day	Common side effects
Verapamil	A	C	240-960 mg	Hypotension, constipation, edema
Lithium	B	C	600-1200 mg	Diarrhea, tremor, polyuria
Topiramate	B	Not rated	50-200mg	Paresthesias, weight loss, cognitive disorder
Methysergide	B	Not rated	1-12 mg	Retroperitoneal fibrosis, nausea, vomiting
Gabapentin	Not rated	Not rated	800-3600 mg	Somnolence, dizziness, weight gain
Melatonin	C	C	10mg	Fatigue, sedation
Sodium valporate	C	B	500-2000mg	Tremor, weight gain, hair loss, nausea

Modified from Robbins et al., Headache. 2016

Pharmacotherapy of PH, SUNCT, HC

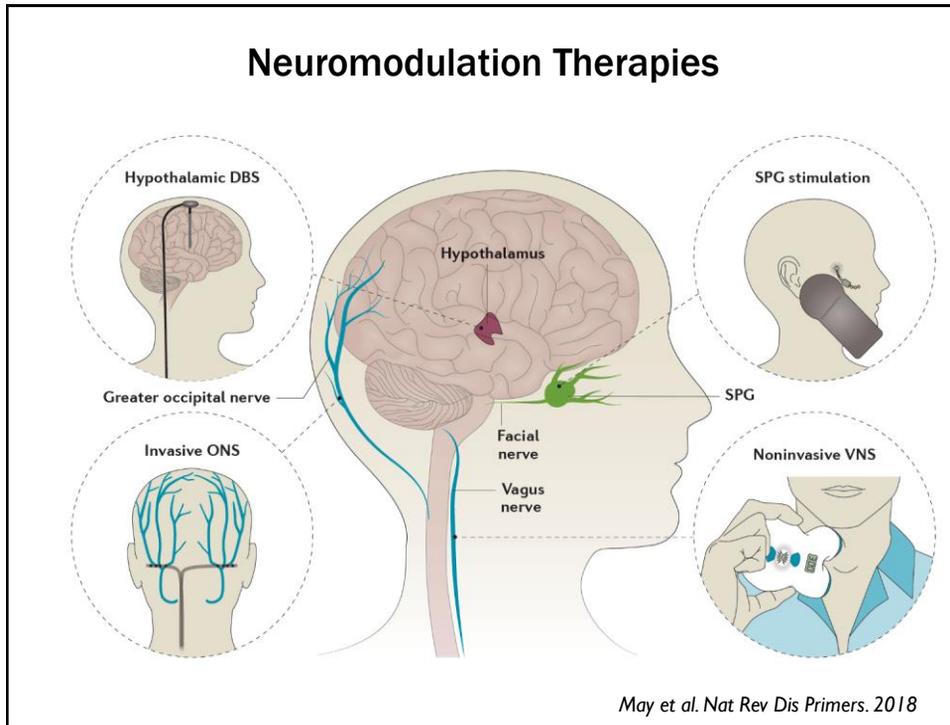
	PH	SUNCT/SUNA	HC
Sumatriptan sc.	20%	Rare effect	No effect
Indomethacin	100%	No effect	100%
Drug of choice	Indomethacin (75-225 mg/day)	Lamotrigine (100-200 mg/day)	Indomethacin (25-300 mg/day)
Second line	Other NSAIDs Verapamil Topiramate	Gabapentin Topiramate	Other NSAIDs Verapamil Topiramate
Others	SPG, GON blocks	Steroids, IV lidocaine	GON blocks, botulinum toxin injection, ONS

Modified from Burish, CONTINUUM (MINNEAP MINN), 2018

Phenotypic and Treatment Outcome on SUNCT and SUNA (III)

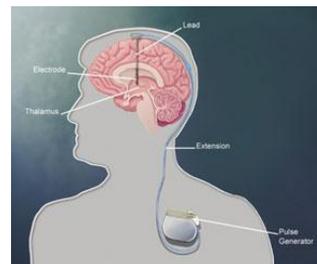
	SUNCT		SUNA	
	Total n	Effective n (100%)	Total n	Effective n (100%)
Lamotrigine	29	18 (62)	16	5 (31)
Topiramate	27	13 (48)	9	1
Gabapentin	29	11 (38)	18	7 (39)
Carbamazepine	43	16 (36)	20	4 (20)
Oxcarbazepine	7	1 (14)	6	0
Pregabalin	7	1 (14)	16	1
Verapamil	16	2 (13)	5	0
Valproate	13	0	4	0
Beta-blocker	7	0	4	0
Tricyclic	36	3	17	3

Modified from Weng et al., Cephalgia. 2018



Deep Brain Stimulation (DBS)

- Refractory chronic CH
- Target: **posterior hypothalamus** → **ventral tegmental area (VTA)**
- Decrease attack frequency in **~60%** of patients
- Stimulation must **continue for weeks or months**, unacceptable response for ongoing CH attacks
- Risks: **hemorrhage, infection**

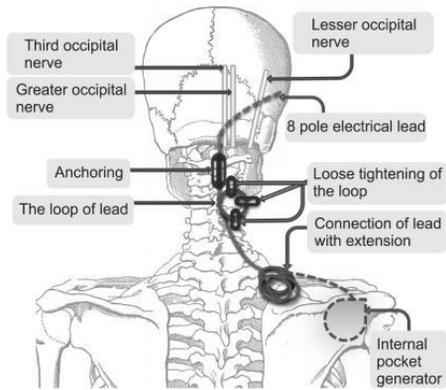


Akram, et al. Neurology, 2016

Clelland et al. Cephalgia. 2014

Occipital Nerve Stimulation (ONS)

- Decrease attack frequency in **~58.1%** of patients (required medication)
- Little or no effect on the **intensity** of attacks or the **duration** of pain
- Side effects: **lead migration, infection, paraesthesia**
- A large multicentre randomized controlled trial is underway (ICON study)

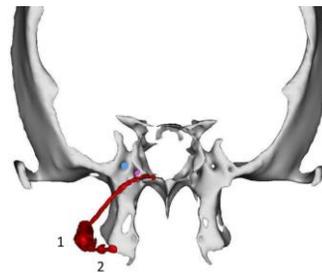


Magis et al. J. Headache Pain. 2016

Wilbrink et al. Cephalalgia. 2013

Sphenopalatine Ganglion (SPG) Stimulation

- In **pterygopalatine fossa**
- The acute responder rate: **32-45%**, decrease attack frequency in **35-55%** of patients
- Adverse events: pain, swelling, hematoma, sensory disturbance (related to surgery, **fully reversible**)
- Long-term effect: unknown



Wei et al. Pract Neurol. 2019

Jurgens et al. Cephalalgia 2017

Noninvasive Vagus Nerve Stimulation (VNS)

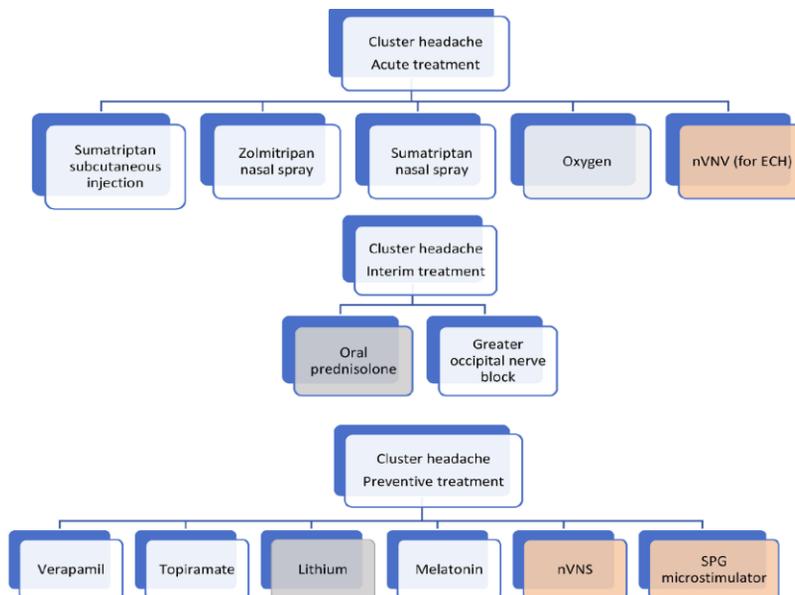
- The **only noninvasive** technique
- **ACT-1,ACT-2:**
acute responder rate: **34-48%**, decrease attack frequency in **~40%** of **episodic CH**
- **The PREVA study:**
add-on therapy in **chronic CH**, higher attack reduction and responder rate than pharmacological prophylaxis
- **US FDA:** acute treatment and prevention



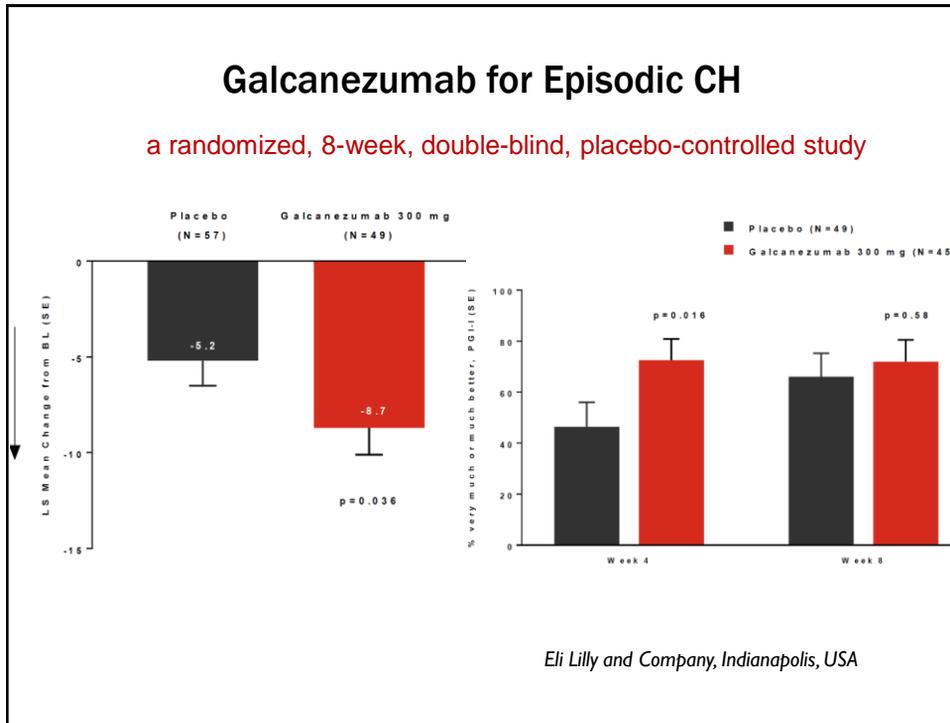
Wei et al. *Pract Neurol*. 2019

Goadsby et al. *Cephalalgia*. 2018

A Landscape of CH Treatment



Wei et al. *Pract Neurol*. 2019



Take Home Messages (I)

- TACs shared characteristics of unilateral headache and ipsilateral cranial autonomic symptoms.
- Anatomical connections between the **hypothalamus**, **trigeminovascular**, and **parasympathetic nervous system** were implicated in the CH pathophysiology.
- Neuroimaging researches suggest CH pathophysiology involve not only the **hypothalamus**, but **pain-modulatory network**, with dynamic changes between the in-bout and out-of-bout periods.
- **CGRP**, **VIP**, and **PACAP38** are good markers of CH attacks, but not specific for CH.

Take Home Messages (II)

- **Oxygen** and **triptans** for acute CH attacks, treatment, **steroids** in transitional prophylaxis, and **Verapamil / Lithium** in prevention.
- **Indomethacin** is effective in PH and HC, while **lamotrigine** is useful for SUNCT.
- **DBS** and **ONS** offer prophylactic benefit in selective chronic CH.
 - **DBS no more used due to mortality.**
- **SPG** stimulation seems to offer both prophylactic and acute CH relief.
- The **US FDA** has approved the **noninvasive VNS** and **galcanezumab** for the treatment of CH.