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. Cephalgia 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. $\geq$1 ipsilateral symptoms or signs:
      a) conjunctival injection or lacrimation
      b) nasal congestion or rhinorrhea
      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 $>\text{half the time}$ 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.

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/extracranial 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*

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**Epidemiology**
Prevalence of Cluster Headache

- **In Westerns**: the prevalence is estimated as
  - 0.01% ~ 0.4% in the general population\(^1\)\(^-\)\(^7\)
  - 8% ~ 10% in a headache clinic population\(^8\)

- **In Asians**: no published data
  - 0.03% (1/3377) (unpublished, Wang SJ, Taipei, 1997)

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### Prevalence Table

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

### Cranial Autonomic Symptoms (CAS)

**Cluster Headache Vs. Migraine**

- **Conjunctival Lacrimation injection**
  - Cluster headache: **p < 0.001**
  - Migraine: **p < 0.001**

- **Nasal congestion**
  - Cluster headache: **p < 0.001**
  - Migraine: **p < 0.001**

- **Rhinorrhea**
  - Cluster headache: **p < 0.001**
  - Migraine: **p < 0.001**

- **Eyelid edema**
  - Cluster headache: **p < 0.001**
  - Migraine: **p < 0.001**

- **Sweating**
  - Cluster headache: **p < 0.001**
  - Migraine: **p < 0.001**

- **Percentage of >1 CAS**
  - Cluster headache: **p < 0.001**
  - Migraine: **p < 0.001**

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**Lai et al., JNNP. 2009**

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<table>
<thead>
<tr>
<th></th>
<th>Taiwan 2003</th>
<th>Japan 2010</th>
<th>China 2013</th>
<th>India 2014</th>
<th>Korea 2017</th>
<th>UK 2002</th>
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<tbody>
<tr>
<td>Numbers</td>
<td>104</td>
<td>86</td>
<td>120</td>
<td>30</td>
<td>200</td>
<td>230</td>
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<tr>
<td>M:F Ratio</td>
<td>6.4:1</td>
<td><strong>3.8:1</strong></td>
<td>7.1</td>
<td>9.1</td>
<td>7.1</td>
<td><strong>2.5:1</strong></td>
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<tr>
<td>CCH (%)</td>
<td>0</td>
<td>3.5%</td>
<td>7.5%</td>
<td>0</td>
<td>0.5%</td>
<td><strong>21%</strong></td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>26.9</td>
<td>31.0</td>
<td>26.7</td>
<td>38</td>
<td>30.7</td>
<td>28.4</td>
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<tr>
<td>Family history</td>
<td>5.8%</td>
<td>--</td>
<td>6.7%</td>
<td>0</td>
<td>--</td>
<td>5.0%</td>
</tr>
<tr>
<td>Predominant laterality</td>
<td>Right</td>
<td>Right</td>
<td>Right</td>
<td>Right</td>
<td><strong>Left</strong></td>
<td>Right</td>
</tr>
<tr>
<td>Most cranial autonomic features</td>
<td>Lacrimation (83%)</td>
<td>Lacrimation (66.3%)</td>
<td>Lacrimation (72.5%)</td>
<td>Lacrimation (83.3%)</td>
<td>Lacrimation (85.5%)</td>
<td>Lacrimation (91%)</td>
</tr>
<tr>
<td>Most additional features</td>
<td>Phonophobia (58%)</td>
<td>Nausea (39.5%)</td>
<td>Nausea (60%)</td>
<td>Phonophobia (40%)</td>
<td>Nausea (48.6%)</td>
<td>Phonophobia (56%)</td>
</tr>
<tr>
<td>Sense of agitation or restlessness</td>
<td>51%</td>
<td>68.9%</td>
<td>38.3%</td>
<td>80%</td>
<td>43.5%</td>
<td><strong>93%</strong></td>
</tr>
<tr>
<td>Aura</td>
<td>1%</td>
<td>--</td>
<td>0</td>
<td>0</td>
<td>0.5%</td>
<td>14%</td>
</tr>
<tr>
<td>Most common time</td>
<td>Midnight (28%)</td>
<td>Nocturnally (47.7%)</td>
<td><strong>7am - 10am, 2pm - 4pm</strong></td>
<td>2pm - 5pm, 12am - 4pm</td>
<td>Night (66.4%)</td>
<td>Nocturnally (73%)</td>
</tr>
</tbody>
</table>
**CAS in cluster headache vs. migraine**

![Graph showing CAS in cluster headache vs. migraine](Lai et al., JNNP. 2009)

**Temperature and Cluster Periods**

CH Periods based on the Taiwan NHI Database from 2005 to 2009

![Graph showing temperature and cluster periods](Lee et al., Cephalagia. 2014)
Comorbidities in patients with CH

- Lung cancer
- Peptic or duodenal ulcer
- Diabetes
- Epilepsy
- COPD
- Stroke
- Cardiac bypass or stent
- Myocardial infarction
- Asthma
- Restless legs
- Sleep apnea
- Depression

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


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., Cephalalgia. 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>
<thead>
<tr>
<th>Country</th>
<th>Affected relatives</th>
<th>Number of affected relatives</th>
<th>Population relative risk (95% CI)</th>
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<tbody>
<tr>
<td></td>
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<td>Observed</td>
<td>Expected</td>
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<tr>
<td>Denmark</td>
<td>First-degree</td>
<td>26</td>
<td>5-40</td>
</tr>
<tr>
<td></td>
<td>Second-degree</td>
<td>10</td>
<td>13-20</td>
</tr>
<tr>
<td>USA</td>
<td>First-degree</td>
<td>41</td>
<td>2-70</td>
</tr>
<tr>
<td>Italy</td>
<td>First-degree</td>
<td>39</td>
<td>2-97</td>
</tr>
<tr>
<td>France</td>
<td>First-degree</td>
<td>22</td>
<td>1-25</td>
</tr>
<tr>
<td></td>
<td>Second-degree</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
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</thead>
<tbody>
<tr>
<td>ADH4 (rs1800759, rs126671)</td>
<td>Rainero, 2010, Zarrili, 2015, Fourier, 2016, Fan, 2018</td>
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<tr>
<td>HCRTR2</td>
<td>Rainero, 2004</td>
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<tr>
<td>Bartsch, 2004</td>
<td></td>
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<td>Schürks, 2006</td>
<td></td>
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<tr>
<td>Baumber, 2006</td>
<td></td>
</tr>
<tr>
<td>Weller, 2015</td>
<td></td>
</tr>
<tr>
<td>Katsarou, 2018</td>
<td></td>
</tr>
<tr>
<td>Fan, 2018</td>
<td></td>
</tr>
<tr>
<td>Fourier, 2019</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial DNA mutation</td>
<td>Cortelli, 1995</td>
</tr>
<tr>
<td>NOS (NOS1, NOS2A, NOS3)</td>
<td>Sjostrand, 2002</td>
</tr>
<tr>
<td>CACNA1A</td>
<td>Sjostrand, 2001</td>
</tr>
<tr>
<td>PER3</td>
<td>Ofte, 2016</td>
</tr>
<tr>
<td>GWAS (ADCYAP1R1, MME)</td>
<td>Bacchelli, 2016, Ran, 2017</td>
</tr>
</tbody>
</table>
Pathophysiology

Pathophysiology of TACs

Trigeminal-autonomic reflex


Neuropeptides

Modified from Riesco et al. Nat Rev Dis Primers. 2018
1. Hypothalamic involvement

PET: May et al. Lancet 1998
MRS: Wang et al. JNNP 2006
VBM: May et al. Nat Med 1999

2. Involvement of Pain Neuromatrix

<table>
<thead>
<tr>
<th>Method</th>
<th>Pain neuromatrix</th>
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<tbody>
<tr>
<td>SPECT</td>
<td>Di Piero et al. 1997</td>
</tr>
<tr>
<td>PET</td>
<td>Hsieh et al. 1996</td>
</tr>
<tr>
<td></td>
<td>May et al. 1998</td>
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<tr>
<td></td>
<td>Sprenger et al. 2004</td>
</tr>
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<td>May et al. 2000</td>
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<tr>
<td></td>
<td>Sprenger et al. 2006, 2007</td>
</tr>
<tr>
<td>fMRI</td>
<td>Morelli et al. 2009</td>
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<tr>
<td></td>
<td>Sprenger et al. 2004</td>
</tr>
</tbody>
</table>

Without acute attacks
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. Cephalalgia 2014

3. Involvement of Other Networks

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


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

  Morelli et al. Cephalalgia 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
  
  Chou et al. Cephalalgia 2017

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**An Integrative View of CH**

- Regions that are altered during acute attacks
- Regions that are altered interictally (between headaches)
- Regions that are altered between cluster-bout periods and out-of-bout periods
- Sensory and nociceptive input from the dural vessels, face and head
- Lacrimation, rhinorrhea and nasal congestion
- Trigeminal nerve
- Parasympathetic division of the facial nerve

May et al. Nat Rev Dis Primers. 2018
A translational model of TACs (I)
Response of 100% oxygen or hexamethonium bromide

A translational model of TACs (II)
Responses of treatments to stimulation of the SuS
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

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

Modified from Robbins et al., Headache. 2016
# Pharmacotherapy of PH, SUNCT, HC

<table>
<thead>
<tr>
<th></th>
<th>PH</th>
<th>SUNCT/SUNA</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan sc.</td>
<td>20%</td>
<td>Rare effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>100%</td>
<td>No effect</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Drug of choice</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(75-225 mg/day)</td>
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</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
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<tr>
<td>(100-200 mg/day)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(25-300 mg/day)</td>
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<tr>
<td><strong>Second line</strong></td>
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<tr>
<td>Other NSAIDs</td>
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<tr>
<td>Verapamil</td>
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<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
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</tr>
<tr>
<td><strong>Others</strong></td>
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<tr>
<td>SPG, GON blocks</td>
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<td></td>
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<tr>
<td>Steroids, IV lidocaine</td>
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<tr>
<td>GON blocks, botulinum toxin injection, ONS</td>
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*Modified from Burish, CONTINUUM (MINNEAP MINN), 2018*

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## Phenotypic and Treatment Outcome on SUNCT and SUNA (III)

<table>
<thead>
<tr>
<th></th>
<th>SUNCT</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Effective n (100%)</td>
<td>Total</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>29</td>
<td>18 (62)</td>
<td>16</td>
</tr>
<tr>
<td>Topiramate</td>
<td>27</td>
<td>13 (48)</td>
<td>9</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>29</td>
<td>11 (38)</td>
<td>18</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>43</td>
<td>16 (36)</td>
<td>20</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>7</td>
<td>1 (14)</td>
<td>6</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>7</td>
<td>1 (14)</td>
<td>16</td>
</tr>
<tr>
<td>Verapamil</td>
<td>16</td>
<td>2 (13)</td>
<td>5</td>
</tr>
<tr>
<td>Valproate</td>
<td>13</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>7</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Tricylic</td>
<td>36</td>
<td>3</td>
<td>17</td>
</tr>
</tbody>
</table>

*Modified from Weng et al., Cephalalgia. 2018*
Neuromodulation Therapies

Deep Brain Stimulation (DBS)

- Refractory chronic CH
- Target: posterior hypothalamus \( \rightarrow \) 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

Clelland et al. Cephalalgia. 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)

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
Goodson et al. Cephalalgia. 2018

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A Landscape of CH Treatment

Wei et al. Pract Neurol. 2019
Galcanezumab for Episodic CH
a randomized, 8-week, double-blind, placebo-controlled study

Eli Lilly and Company, Indianapolis, USA

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.