Trigeminal Autonomic Cephalgia

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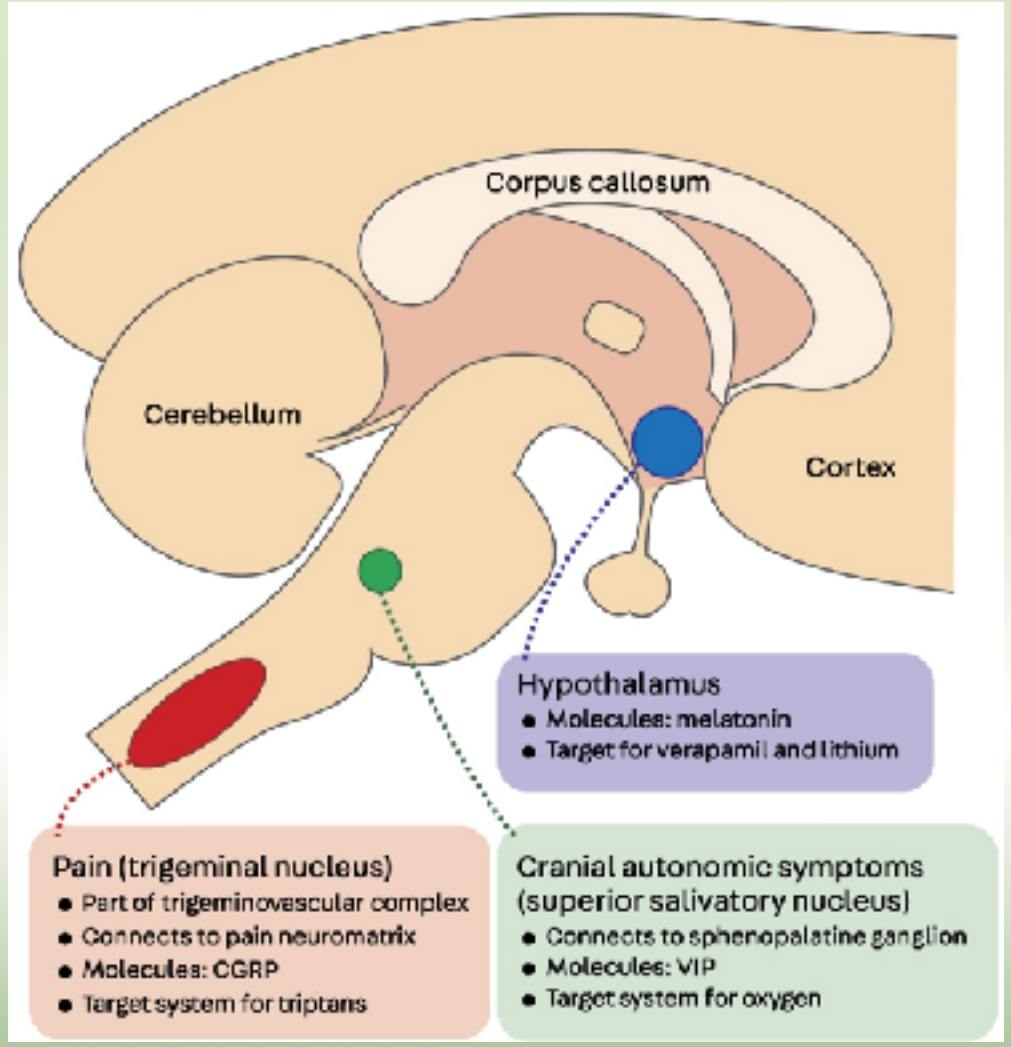
Objectives

- Discuss the pathophysiology of Trigeminal Autonomic Cephalgia
- Discuss variants of trigeminal autonomic cephalgia and the ICHD-3 classification for:
  - Cluster
  - Paroxysmal hemicranias
  - SUNCT
  - Hemicrania Continua
- Review the mechanism of action, side effects, utility and proper selection of abortive and prophylactic therapy for cluster headaches
- Review the mechanism of action, side effects, utility and proper selection of abortive and prophylactic therapy for other forms of Trigeminal Autonomic Cephalgia

TRIGEMINAL AUTONOMIC CEPHALGIA PATHOPHYSIOLOGY

Pathogenesis

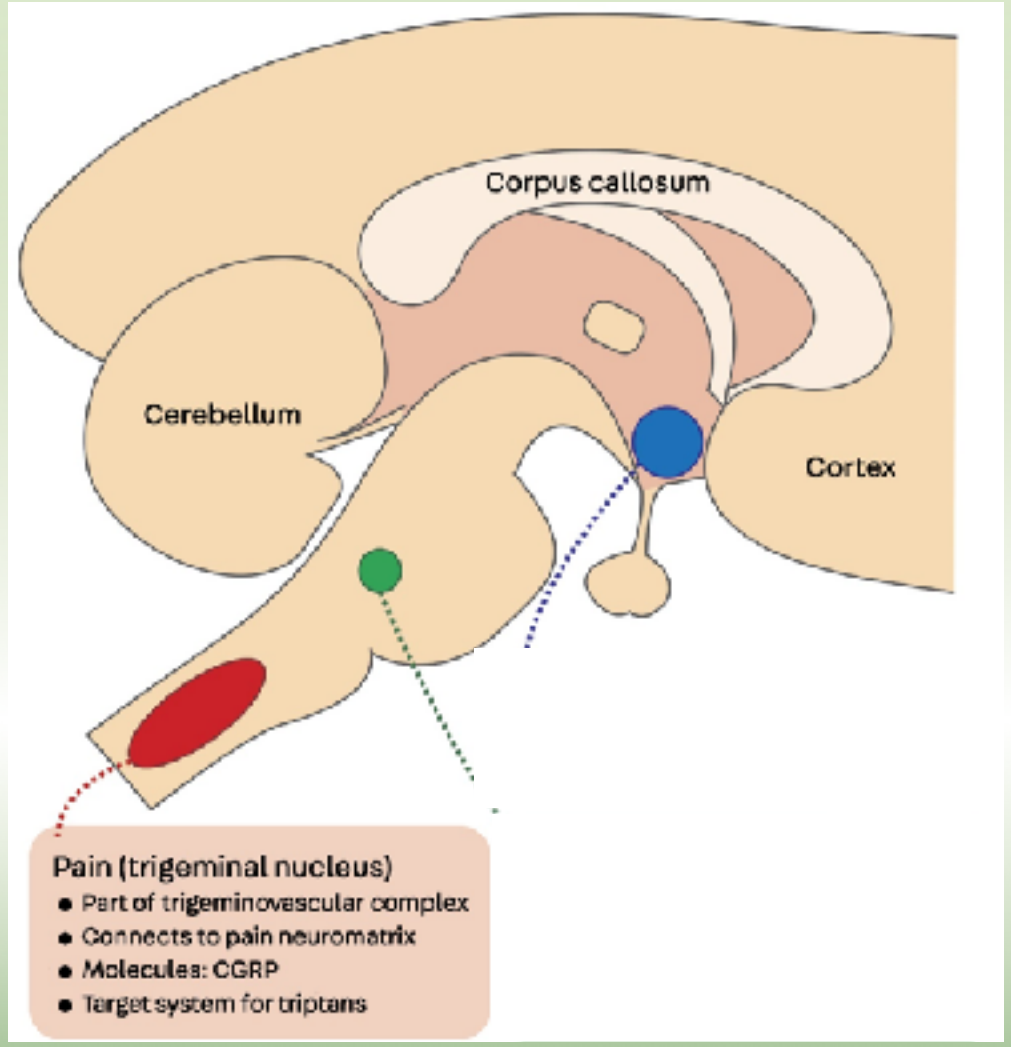
- Three systems are interconnected
  - Pain System
  - Cranial Autonomic System
  - Hypothalamus



Pathogenesis of trigeminal autonomic cephalalgias. At least three systems are involved including the pain system (the trigeminal nerve, trigeminovascular complex, and general pain system called the pain neuromatrix), the cranial autonomic system (the superior salivatory nucleus and sphenopalatine ganglion), and the hypothalamus.

Pain System

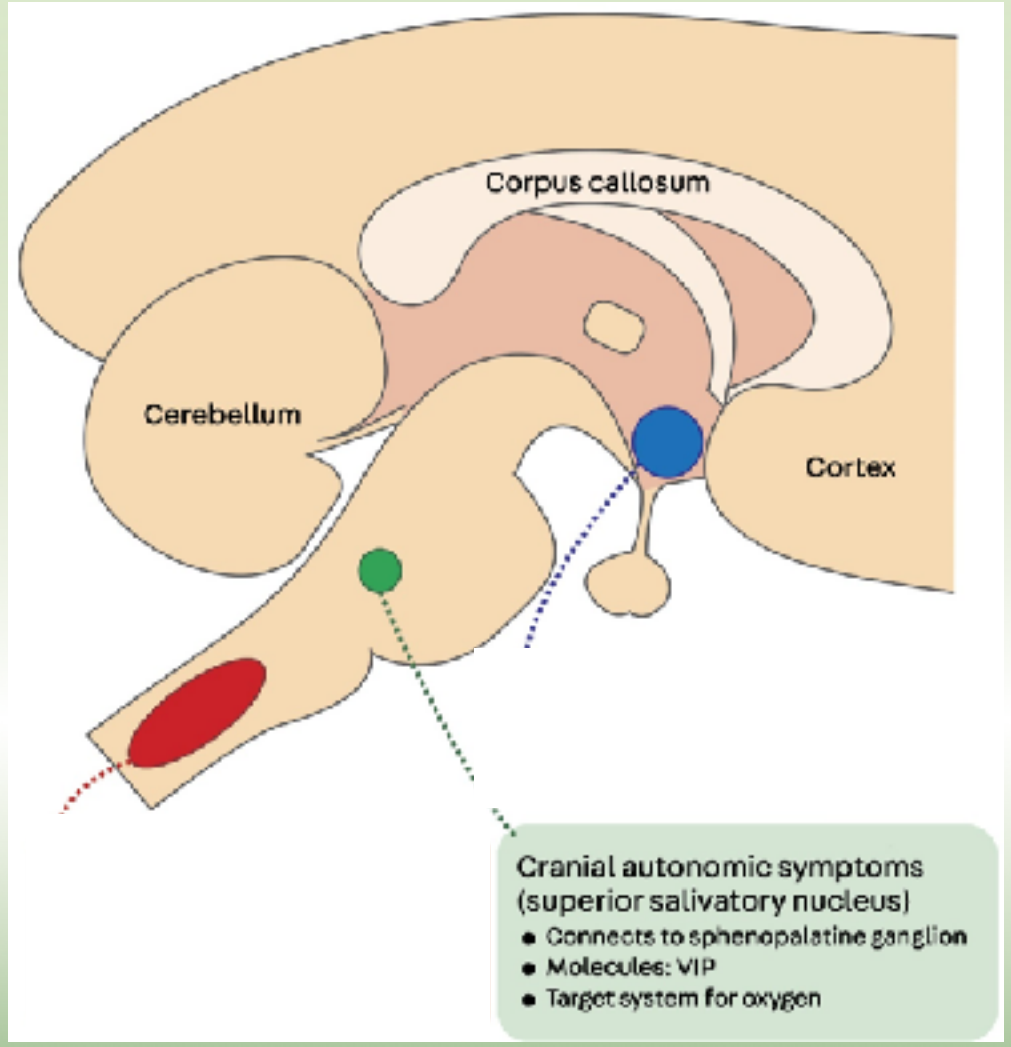
- Composed of the trigeminal nerve, trigeminovascular complex, and general pain system called the pain neuromatrix
  1. The trigeminovascular system is the pain component of and starts with the ophthalmic or V1 branch of the trigeminal nerve, which receives inputs from the forehead, eye, dura, and large cranial vessels.
  2. The ophthalmic branch projects to several nociceptive nuclei in the brainstem and upper cervical cord (together these nuclei are known as the trigeminocervical complex, which includes the occipital nerve), then to the thalamus, and finally to the pain neuromatrix
- Target for **triptans** and **CGRP** modulating drugs



Pathogenesis of trigeminal autonomic cephalalgias. At least three systems are involved including the pain system (the trigeminal nerve, trigeminovascular complex, and general pain system called the pain neuromatrix).

Autonomic System

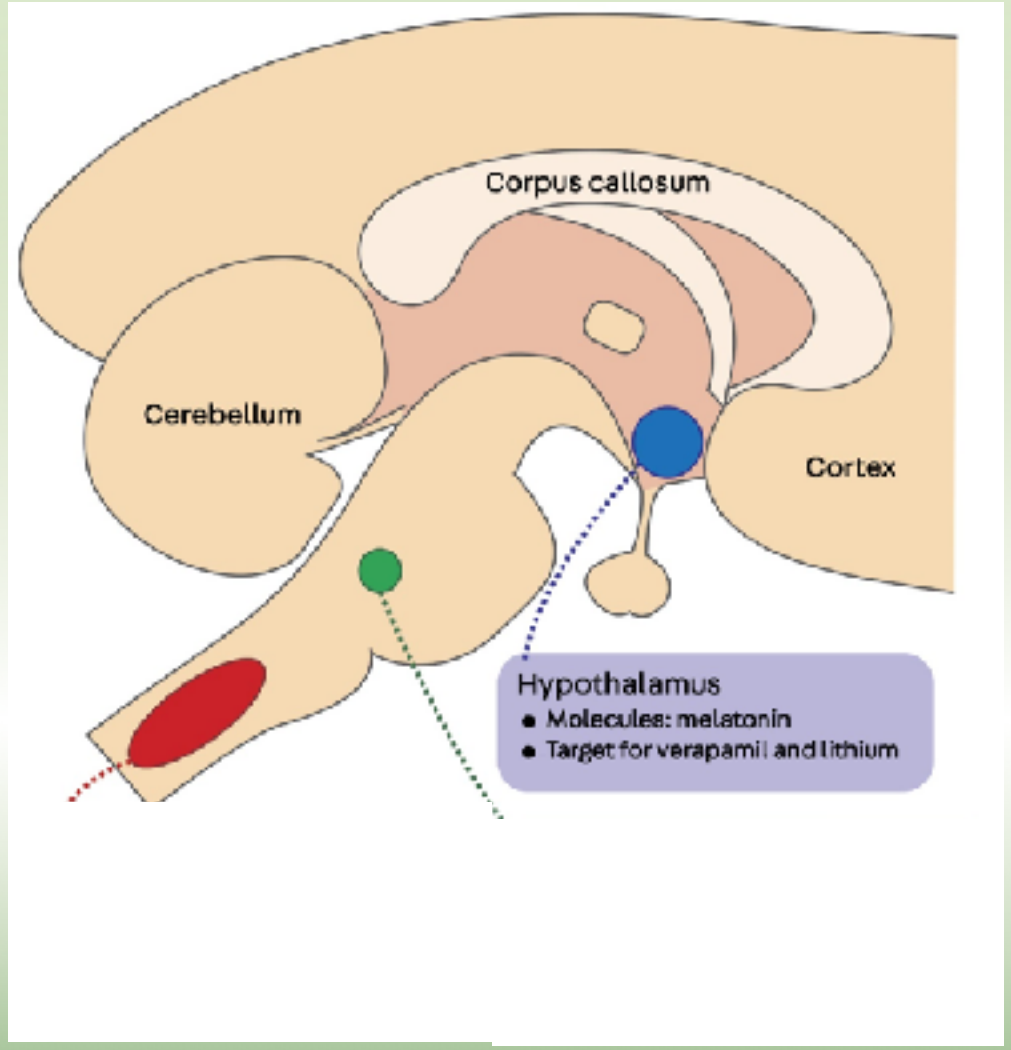
- The autonomic system is responsible for lacrimation, conjunctival injection, sweating
  - Due to parasympathetic overactivation or sympathetic inactivation.
  - The autonomic symptoms arise from the superior salivatory nucleus to the sphenopalatine ganglion connections
- <u>This is the targeted system for **Oxygen** use in cluster headaches</u>



Pathogenesis of trigeminal autonomic cephalalgias. At least three systems are involved including the cranial autonomic system (the superior salivatory nucleus and sphenopalatine ganglion)

Hypothalamus

- First area activated during a cluster attack, followed by trigeminovascular and then autonomic activation.
- Molecules modulated by the hypothalamus, such as melatonin are altered in TAC's
- Includes the circadian system and aggression areas, which may explain the clocklike regularity of cluster headache.
- This is the targeted system for **Verapamil** and **Lithium** use in cluster headaches



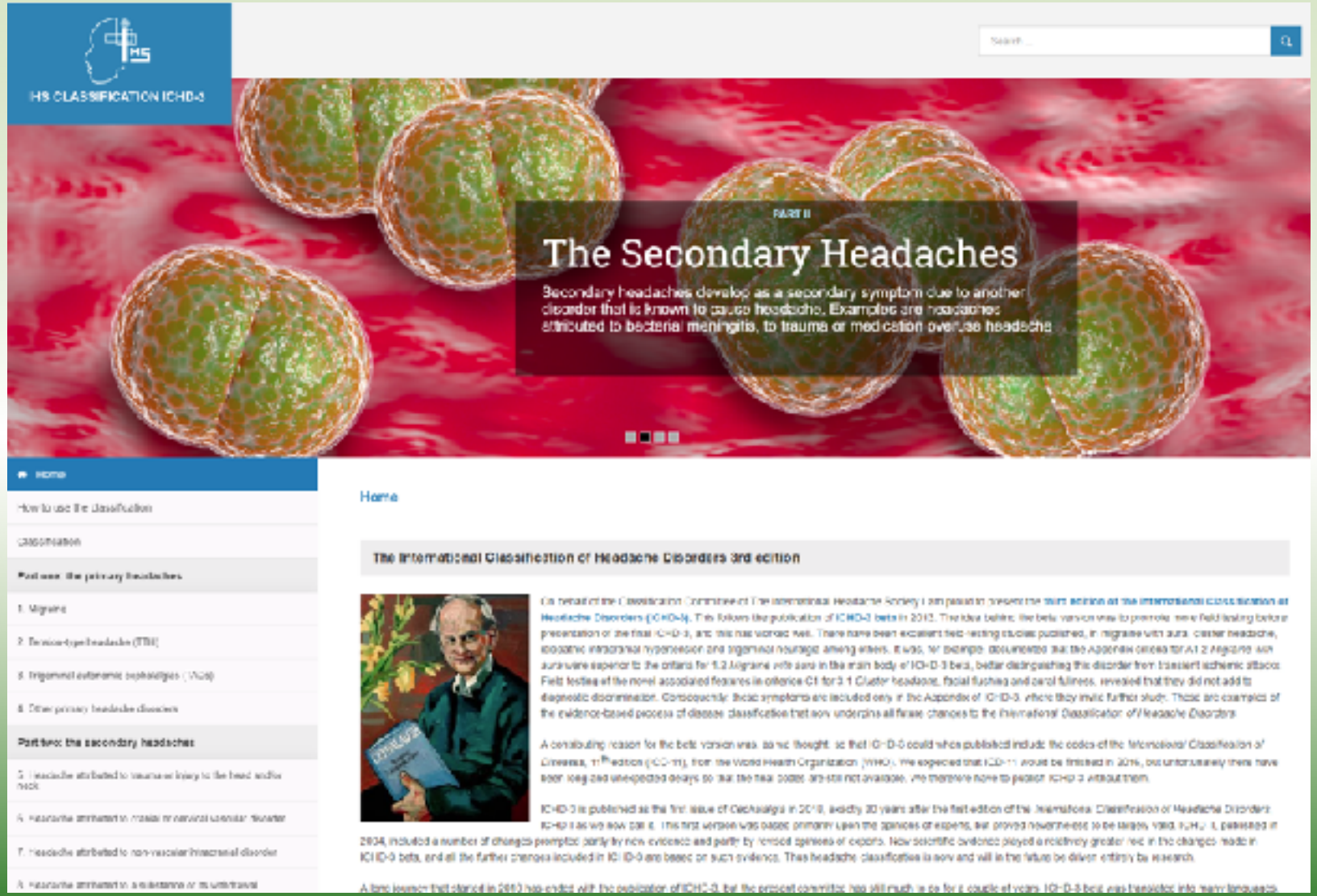
Pathogenesis of trigeminal autonomic cephalalgias. At least three systems are involved including the hypothalmus

CLUSTER HEADACHES

Epidemiology

- Age of onset: 20-40 y/o
- 3x Men>Women
- Two forms:
  - Episodic- pain free intervals of more than three months (>90% of cases)
  - Chronic-pain free intervals <3 months

ICHD-3


IHS CLASSIFICATION ICHD-3
PART II
The Secondary Headaches
Secondary headaches develop as a secondary symptom due to another disorder that is known to cause headache. Examples are headaches attributed to bacterial meningitis, to trauma or medication overuse headache
Home
How to use the classification
Classification
Part one: the primary headaches
1 Migraine
2 Tension-type headache (TTH)
3 Trigeminal autonomic cephalalgias (TACs)
4 Other primary headache disorders
Part two: the secondary headaches
5 Headache attributed to trauma or injury to the head and/or neck
6 Headache attributed to cranial or cervical vascular disorder
7 Headache attributed to non-vascular intracranial disorder
8 Headache attributed to a substance or its withdrawal
Home
The International Classification of Headache Disorders 3rd edition

Cluster ICHD-3 Criteria

- Cluster Headache
  - A. At least five attacks fulfilling criteria B–D
  - B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 minutes (when untreated)
  - C. Either or both of the following:
    1. At least one of the following symptoms or signs, ipsilateral to the headache:
       a) Conjunctival injection and/or lacrimation
       b) Nasal congestion and/or rhinorrhea
       c) Eyelid edema
       d) Forehead and facial sweating
       e) Miosis and/or ptosis
    2. A sense of restlessness or agitation
  - D. Occurring with a frequency between one every other day and eight per day
  - E. Not better accounted for by another ICHD-3 diagnosis

Episodic vs. Chronic Cluster

Episodic Cluster Headache

A. Attacks fulfilling criteria for cluster headache and occurring in bouts with at-least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of **≥3 months**

Chronic Cluster Headache

- Attacks fulfilling criteria for cluster headache and occur without a remission period, or with remissions lasting **<3 months, for at least 1 year**

Cluster Clinical Features

- Symptoms are intensely unpleasant, with pain that is anecdotally worse than migraine, childbirth, or kidney stones.
- The most peculiar feature of cluster headache, however, may be its clocklike regularity.
- Triggers include alcohol, nitroglycerin, heat/ exercise, high altitude (such as plane flights), and strong smells like solvents and cigarette smoke.

Acute Management

- High flow oxygen via 100% nonrebreather mask at 12L/min for 20 minutes
- Triptans- preferably injectable Sumatriptan given fast time of onset.
- Greater occipital nerve blocks
  - Shown to be beneficial in acute prevention (just before or early in onset of symptoms) of predictable episodic cluster

Prophylaxis Management

- Oral Prednisone
  - Three week course just before or at onset of cluster
- Verapamil
  - Goal dose of 480-720mg in divided doses (much higher than typical dosing)
    - Watch for PR prolongation
      - Obtain baseline EKG and routine follow-ups with dosing changes
- Lithium
  - Used in Verapamil Failures
- Others
  - Mixed data on Topiramate, Baclofen and Melatonin

	American Headache Society Recommendations[27]	European Federation of Neurological Societies Recommendations[28]
Acute		
Oxygen (high flow)	Level A	Level A
Sumatriptan subcutaneous	Level A	Level A
Sumatriptan nasal	Level B	Level A
Sumatriptan oral		
Zolmitriptan nasal	Level A	Level A/level B
Zolmitriptan oral	Level B	Level B
Octreotide subcutaneous	Level C	Level B
Lidocaine nasal	Level C	Level B
Noninvasive vagus nerve stimulation		
Transitional		
Ipsilateral greater occipital nerve block	Level A	
Oral steroids	Level U	Level A
Ergotamine tartrate		Level B
Preventive		
Verapamil	Level C	Level A
Lithium	Level C	Level B
Melatonin	Level C	Level C
Topiramate		Level B
Baclofen		Level C
Valproic acid	Unfavorable[b]	Level C
Refractory		
Sphenopalatine ganglion stimulation	Level B	
Occipital nerve stimulation		
Hypothalamic deep brain stimulation	Unfavorable[b]	

Level A = established as effective; level B = probably effective; level C = possibly effective; level U = data inadequate.

[a] Blank entries indicate that no specific recommendation is provided.

[b] Valproic acid and hypothalamic deep brain stimulation are probably ineffective according to American Headache Society guidelines (level B negative rating).

PAROXYSMAL HEMICRANIA

Epidemiology

- Age of onset: 30-40 y/o
- Slightly more common in females
- Symptoms tend to be chronic rather than episodic

Paroxysmal Hemicrania ICHD-3 Criteria

- Paroxysmal Hemicrania
  - A. At least twenty attacks fulfilling criteria B–E
  - B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 2-30 minutes
  - C. Either or both of the following:
    1. At least one of the following symptoms or signs, ipsilateral to the headache:
       a) Conjunctival injection and/or lacrimation
       b) Nasal congestion and/or rhinorrhea
       c) Eyelid edema
       d) Forehead and facial sweating
       e) Miosis and/or ptosis
    2. A sense of restlessness or agitation
  - D. Occurring >5 times per day
  - E. Prevented absolutely by therapeutic dosing of indomethacin
  - F. Not better accounted for by another ICHD-3 diagnosis

Paroxysmal Hemicrania Clinical Features

- Symptoms are intensely unpleasant pain described as generally sharp, stabbing, or throbbing and is located in the orbital, supraorbital, and temporal area.
- Triggers include alcohol, neck movements, or pressure over the neck or greater occipital nerves.

Management

- Indomethacin
  - Up-titrate from25 mg 3 times a day to 75 mg 3 times a day over 1 to 2 weeks, then to stay at 75 mg 3 times a day for another 1 to 2 weeks.
  - Common Side effects
    - nausea, dyspepsia, diarrhea or constipation.
    - Offer GI prophylaxis with H2 Blocker or PPI
- Once the patient's headaches improve, a reduction in the dosage is suggested to find the minimal effective dose, which is often less than a total daily dose of 100 mg.

SUNCT (SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE ATTACKS WITH CONJUNCTIVAL INJECTION AND TEARING)

Epidemiology

- Rare
- Age of onset: 40-70 y/o
- Slightly more common in men
- Can be either episodic or chronic

SUNCT ICHD-3 Criteria

- SUNCT
  - A. At least twenty attacks fulfilling criteria B–D
  - B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 1-600 seconds occurring in single stabs, series or stabs or a sawtooth pattern
  - C. Either or both of the following:
    1. Conjunctival injection and lacrimation ipsilateral to the head
    2. At least one of the following symptoms or signs, ipsilateral to the headache:
       - a) Nasal congestion and/or rhinorrhea
       - b) Eyelid edema
       - c) Forehead and facial sweating
       - d) Miosis and/or ptosis
  - D. Occurring >1 times per day
  - E. Not better accounted for by another ICHD-3 diagnosis

Management

- Lamotrigine
  - goal dose between 100 mg and 200 mg.
- Second-line
  - Topiramate, gabapentin, carbamazepine, oxcarbazepine, or duloxetine.

HEMICRANIA CONTINUA

Epidemiology

- Very Rare
- Slightly more common in women

Hemicrania Continua ICHD-3 Criteria

- Hemicrania Continua
  - A. Unilateral headache fulfilling criteria B–D
  - B. Present for >3 months
  - C. Either or both of the following ipsilateral to the headache:
    1. At least one of the following symptoms or signs, ipsilateral to the headache:
       a) Conjunctival injection and lacrimation
       b) Nasal congestion and/or rhinorrhea
       c) Eyelid edema
       d) Forehead and facial sweating
       e) Miosis and/or ptosis
    2. Sense of restless, agitation or aggravation of pain by movement
  - D. Responds absolutely to therapeutic dose of indomethacin
  - E. Not better accounted for by another ICHD-3 diagnosis

Hemicrania Continua Clinical Features

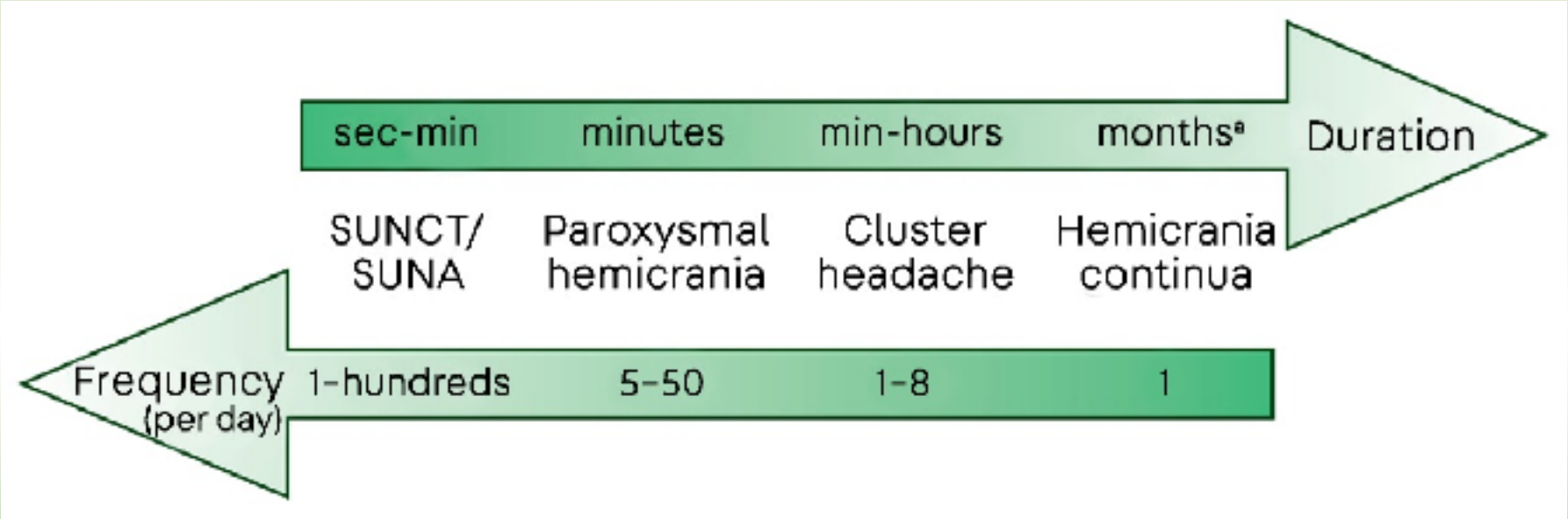
- Unilateral frontal or temporal pain that is usually sharp or throbbing in nature.
  - Foreign body sensation or itching of the affected eye.
  - Punctuated by headache flares lasting minutes to days that are associated with an increase in ipsilateral cranial
  - Autonomic features as well as the presence of nausea, photophobia, or phonophobia.
- In comparison with other TACs, hemicrania continua has less prominent cranial autonomic features and more prominent migrainous features.
- Triggers for flares include stress, alcohol, and irregular sleep.

Management

- Indomethacin
  - Up-titrate from25 mg 3 times a day to 75 mg 3 times a day over 1 to 2 weeks, then to stay at 75 mg 3 times a day for another 1 to 2 weeks.
  - Common Side effects
    - nausea, dyspepsia, diarrhea or constipation.
    - Offer GI prophylaxis with H2 Blocker or PPI
- Once the patient's headaches improve, a reduction in the dosage is suggested to find the minimal effective dose, which is often less than a total daily dose of 100 mg.

COMPARING TRIGEMINAL AUTONOMIC CEPHALGIA ATTACK TIMING

Timing of individual attacks in trigeminal autonomic cephalalgias



TRIGEMINAL AUTONOMIC CEPHALGIA CLINICAL AND TREATMENT SUMMARY

	Cluster Headache[1]	Paroxysmal Hemicrania[2]	SUNCT/SUNA[3]	Hemicrania Continua[4]
Ratio of female to male	1:5	Slightly more female	1:1.5	2:1
Pain				
Quality	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Baseline: aching; exacerbations: sharp, stabbing, throbbing
Severity	Very severe	Very severe	Severe	Baseline: mild to moderate; exacerbations: moderate to severe
Attacks				
Frequency (per day)	1–8[a]	5–50	1 to hundreds	Constant
Duration (minutes)	15–180	2–30	0.01–10[b]	Baseline: 6 months or more; exacerbations: 30 minutes to 3 days
Ratio of episodic to chronic	90:10	35:65	10:90	15:85[c]
Associated features				
Restlessness	90%	80%	65%	70%
Circadian periodicity	82%[5]	Rare	Rare	Rare
Triggers				
Alcohol	Yes	Yes	No	Yes
Nitroglycerin	Yes	Yes	No	Rare
Neck movements	No	Yes	Yes	No
Cutaneous	No	No	Yes	No
Treatment response				
Oxygen	70%	No effect	No effect	No effect
Sumatriptan 6 mg subcutaneous	90%	20%	Rare effect	No effect
Indomethacin	Rare effect	100%	No effect	100%

SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

[a] Cluster headache frequency is officially one headache every other day up to eight per day.[1]

[b] SUNCT and SUNA duration is 1 to 600 seconds.

[c] For hemicrania continua, the ratio of episodic to chronic refers to the ratio of remitting to unremitting attacks.