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Trigeminal Autonomic Cephalalgias

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Learning Objectives

Upon completion of this activity, learners will be able to:

- Outline an approach to the history, examination, investigation, and treatment of a patient with a trigeminal autonomic cephalalgia (TAC);
- Apply lessons learned from using cluster headache as a model TAC to better understand the other TACs;
- Summarize evidence-based treatment strategies for TACs, recognizing that approved treatments for some TACs are scant.

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Case 1: 50-year-old Female

- Referred for “migraine”
- 15-year history of headaches from September-November
- Pain is always behind left eye
- Attacks usually awaken her from sleep and last 60-90 minutes
- During attacks, she paces around the room
- Left eye photophobia during attacks
- In autumn, any alcohol leads to an “instant headache”

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Case 1: 50-year-old Female

What is the most likely diagnosis?

A. Chronic migraine without aura

B. Episodic cluster headache

C. Chronic cluster headache

D. Hypnic headache

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Case 1: 50-year-old Female

- 50 year-old female referred for “migraine” — Misdiagnosis of TACs common especially in women
- 15-year history of headaches from September-November — Circannual and circadian clustering
- Pain is always behind left eye — Side-locked
- Attacks usually awaken her from sleep and last 60-90 minutes — Relatively short
- During attacks, she paces around the room — Restlessness
- Left eye photophobia during attacks
- In autumn, any alcohol leads to an “instant headache”

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Trigeminal Autonomic Cephalalgias (TACs)

- Short-lasting headaches caused by activation of the trigeminal-parasympathetic reflex arc
- Unilateral (usually side-locked), severe headaches with ipsilateral trigeminal autonomic features

Note: up to 50% of patients with migraine may report autonomic features, but these are more typically bilateral

Burish M. Continuum 2024
Hoffman J and May A. Lancet Neurol 2018
Leone M and Bussone G. Lancet Neurol 2009

Picture taken from Nesbitt A and Goadsby PJ. BMJ 2012

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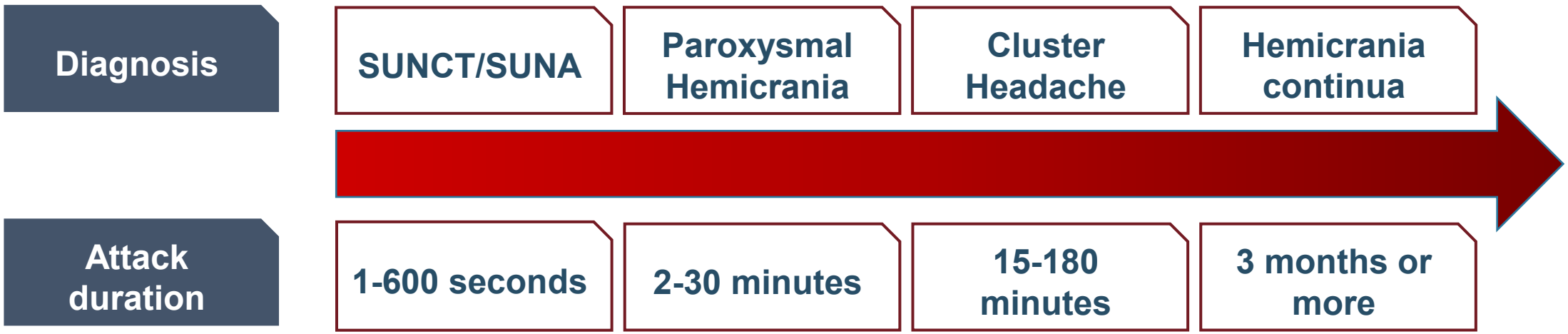
What are the TACs?



- The shorter the attack, the more per day (SUNCT: 1-hundreds/day)
- The longer the attack, the fewer per day (cluster: every 2 days-8/day)
- Note the potential overlap between duration

ICHD-III, Cephalalgia 2018

SUNCT: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
SUNA: Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms

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TAC History

- Duration and frequency of attacks
  - Short attacks? Sawtooth pattern? Pain-free or remission periods?
- Assess for unilaterality and side-locked nature
- Dig deep into autonomic symptoms
  - Assess for sense of restlessness - very atypical for migraine
- Attack timing, in particular circadian or circannual clustering
- Triggers
  - Cluster headache: alcohol, smoking, nitroglycerin, strong smells

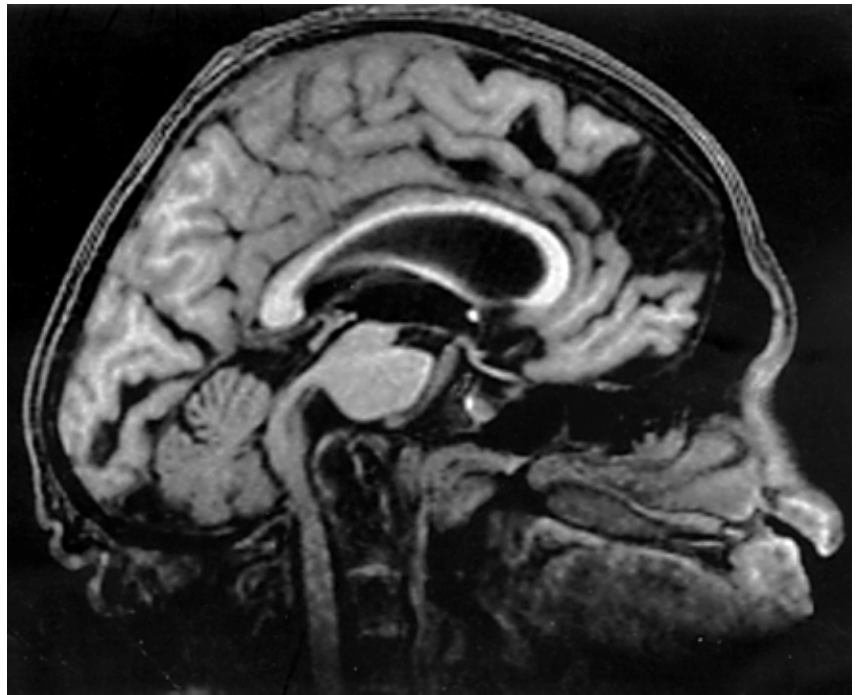
Note: migrainous features may be present in cluster and PH/HC or more rarely in SUNCT/SUNA, but are more commonly ipsilateral to pain

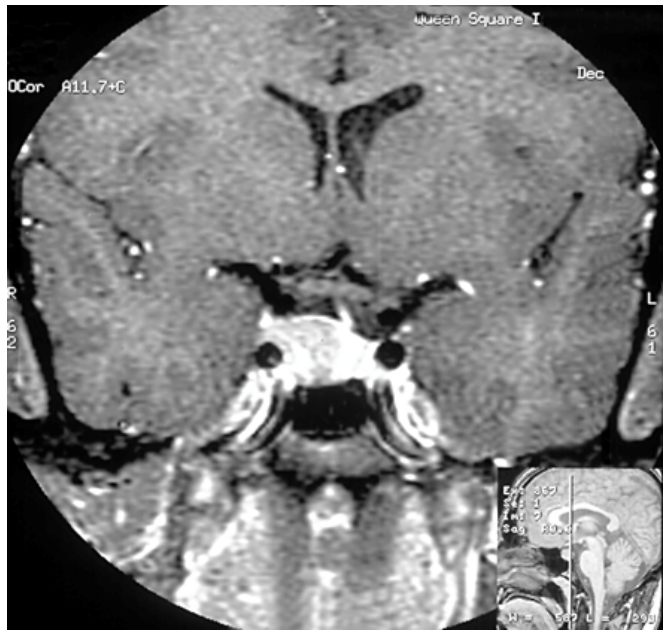
- **Migrainous features: photophobia/phonophobia, nausea**

Irimia P. et al. Cephalalgia 2008
Snoer A.H. et al. Eur J Neurol 2019

TAC Differential Diagnosis

- **Primary headache disorders**
  - Migraine
  - Hypnic headache
  - Primary stabbing headache
- **Secondary causes of a TAC-like headache**
  - **Pituitary tumors**
  - **Posterior fossa lesions**
  - Vascular dissection or AVM
  - Obstructive sleep apnea
- **Secondary TAC mimics**
  - Glaucoma
  - Temporal arteritis
  - Trigeminal neuralgia
  - Sinusitis





Burish M. Continuum 2024
Matharu M. et al. J Neurol Neurosurg Psychiatry 2003
Berg J and Goadsby P. J Neurol Neurosurg Psychiatry 2001

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TAC Investigations

- All patients: MRI brain including pituitary/hypothalamus and cavernous sinus views
- Most patients: MRA head and neck
- All patients: Pituitary laboratory studies (consider TSH, prolactin, GH, testosterone)
- Selected patients:
  - MR venogram (especially in hemicrania continua)
  - Trigeminal nerve imaging (especially in SUNCT/SUNA)
  - Sleep study
  - ESR
  - Dentistry/ENT referral
  - Lung imaging if Horner's syndrome and/or smoker

Mitsikostas DD et al. J Headache Pain 2015

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ICHD-III Cluster

Criteria for each TAC

- **Unilateral pain**
- **At least one autonomic symptom**
  - Restlessness/agitation counts
  - Exception: SUNCT (need both conjunctival injection AND tearing)
- **Not due to another ICHD-3 diagnosis**
- **Episodic and chronic forms**
  - Episodic: remission periods over 3 months
  - Chronic: no remission longer than 3 months
  - Exception: HC – remitting subtype has ≥24 hour pain-free periods

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[b]

E Not better accounted for by another *ICHD-3* diagnosis

Episodic Cluster Headache

A Attacks fulfilling criteria for cluster headache and occurring in bouts (cluster periods)

B 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

A Attacks fulfilling criteria for cluster headache and criterion B below

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

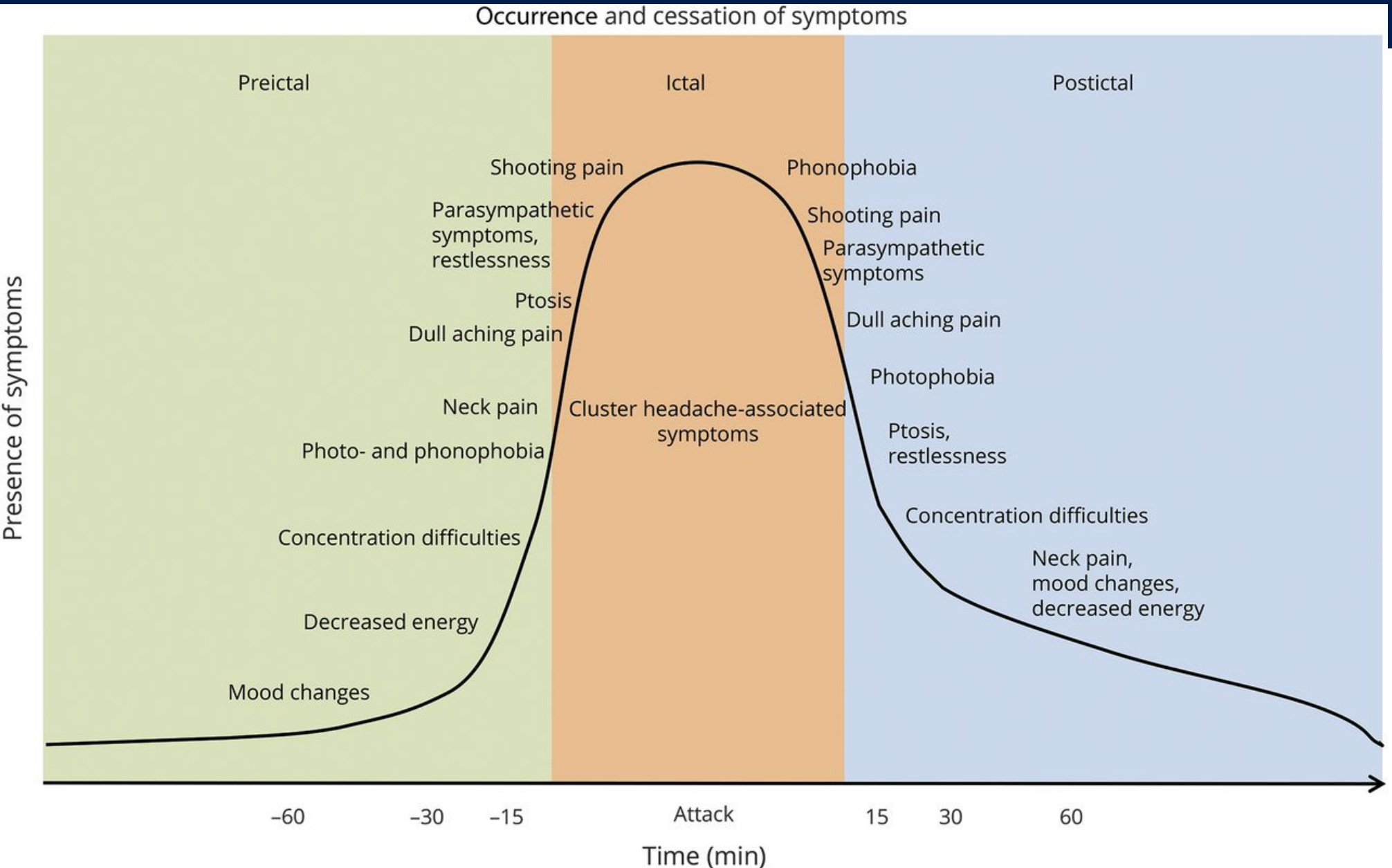
ICHD-3 = International Classification of Headache Disorders, Third Edition.

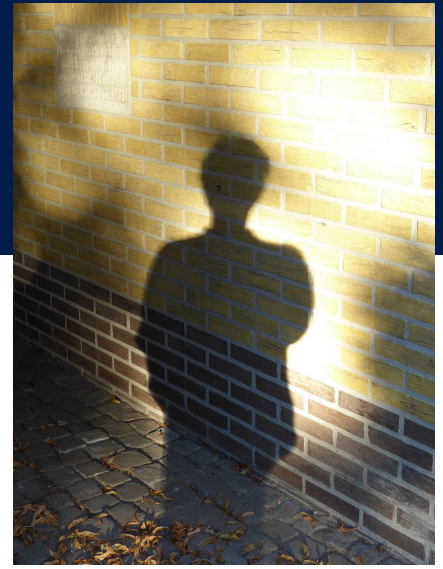
[a] Reprinted with permission from Headache Classification Committee of the International Headache Society, Cephalalgia.[6] © 2018 International Headache Society.

[b] During part but less than half of the active time course of cluster headache, attacks may be less frequent.

Burish M. Continuum 2024

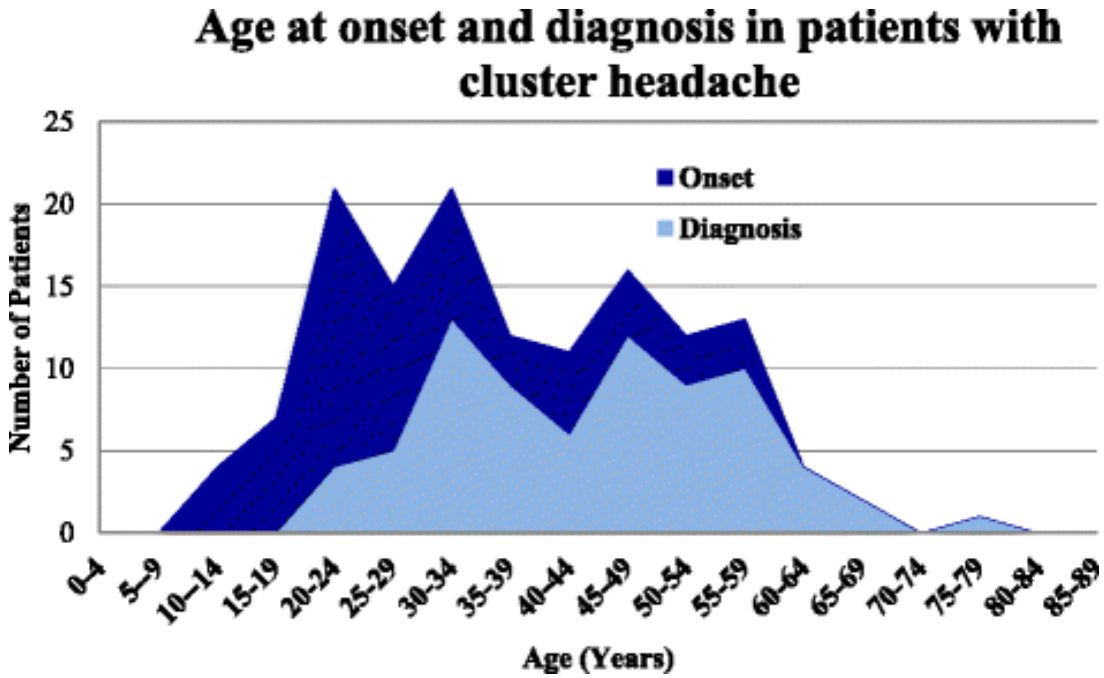
Cluster Attack Timeline





Cluster Epidemiology

- Lifetime prevalence 0.12% (more common than MS in some places!)
- Male:female ratio decreasing over time
  - 4.3:1 in 2008 meta-analysis
  - 1.3-2.6 in more recent studies
  - ?True shift or misdiagnosis in women
- Positive family history in 6.3-8.2%
- Average diagnostic delay 5-13 years



Schindler E. and Burish M. BMJ 2022;
Joshi S et al. J Headache Pain 2017.

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TABLE 5-4

Evidence-based Guidelines for the Treatment of Cluster Headache From the American Headache Society[a]

Guidelines are old (2016)!

High-flow oxygen = 100% O2 at 10-15L for 15-20 minutes via non-rebreather mask

	Acute	Preventive
Level A use	Subcutaneous sumatriptan, zolmitriptan nasal spray, 100% oxygen	Suboccipital steroid injection
Level B use	Sumatriptan nasal spray, oral zolmitriptan	Zucapsaicin nasal spray (not currently available in the United States)
Level C use	Lidocaine nasal spray, subcutaneous octreotide	Lithium, verapamil, warfarin, melatonin
Level A do not use	None	None
Level B do not use	None	Sodium valproate, sumatriptan, deep brain stimulation
Level C do not use	None	Cimetidine/chlorpheniramine, misoprostol, hyperbaric oxygen, candesartan
Level U	Dihydroergotamine nasal spray, somatostatin, prednisone	Frovatriptan, intranasal capsaicin, nitrate tolerance, prednisone

[a] Data from Robbins MS, et al, Headache.[26]

Nahas SJ Continuum 2021; Wei D. et al. Pract Neurol 2019; Robbins M. et al. Headache 2016; Goadsby PJ et al. Cephalalgia 2018; Goadsby PJ et al. N Engl J Med 2019

Cluster Prevention

New European guidelines 2023

Procedures

Intervention	Evidence	Recommendation
nVNS	Low level of evidence for episodic cluster Low level of evidence for chronic cluster	Strong Low adverse event profile[a] Noninvasive[a] No interactions[a]
GON block	Consensus statement[b]	Consensus
GON stimulation	Consensus statement[b]	Consensus
SPG stimulation	Moderate level of evidence	Strong

TABLE 17 Summary of recommendations for preventive medication for cluster headache.

Substance	Evidence	Recommendation	Effect/comments
Verapamil	Consensus statement[a]	Consensus	• Preventive method of choice in episodic and chronic cluster • Efficacy reached depending on dosage after 2–3 weeks or prior experience • In most cases, no complete suspense of attacks • Prednisone to bridge time until efficacy reached
Oral corticosteroids	Low level of evidence	Weak	• Additional to bridge time until verapamil is efficacious • Efficacious in 70%–80% of patients • Gastric protection required • Avoid prolonged treatment regimes
Galcanezumab	Low level of evidence	Weak	One positive RCT for episodic but not chronic cluster headache
Lithium	Consensus statement[a]	Consensus	• Some studies indicate a similar efficacy to verapamil (70%) • Side effect, therefore only chosen if other medications are contraindicated or failed (chronic cluster) • Efficacy reached within 1–2 weeks
Topiramate	Consensus statement[a]	Consensus	• No valid trials but open label case series indicating positive effect • Efficacious after 2–3 weeks
Ergotamine-tartrate	Consensus statement[a]	Consensus	• Efficacious in 70% • In combination with antiemetic medication • Short-term prophylaxis and to bridge time until verapamil effect sets in • In patients with attacks during the night
Frovatriptan	Consensus statement[a]	Consensus	Short-term prophylaxis and in patients with attacks during the night
Valproic acid	Consensus statement[a]	Consensus	• Only one trial indicating preventative efficacy • Can be used if other medication has failed (method of third choice) • Influenced circadian rhythm in animal studies; reduces GABA activity • Reaching efficacy can take up to 4 weeks
Melatonin	Consensus statement[a]	Consensus	• Can be used if other medication has failed (method of third choice) • Can be tried in patients with sleep problems

Can see rebound on wean

May A et al. Eur J Neurol 2023;30:2955-2979.

Why Use Preventive Therapy for Cluster Headache?

- Goal-setting is very important
- Preventives are not intended to stop attacks as they happen
- Preventive goals
  - Decrease attack frequency and maybe duration
  - Decrease attack severity
  - Shorten bout duration
  - ?Reduce progression to chronic cluster

Assessing Cluster Preventive Efficacy

- Natural history of cluster makes assessment difficult
- Bout duration may vary year to year
- Some patients have very predictable attack periods and durations
- Some patients may skip a year
- Shared decision-making is crucial

Starting and Stopping Preventives for Cluster

- Benefit more likely if preventive is started ASAP at bout onset
  - With predictable bout onset, reasonable to start preventive 1-2 weeks before expected first attack
  - Otherwise start ASAP at first premonitory sensations or first attack
- Onset of efficacy in cluster may be faster than in migraine at 1-3 weeks
- Patients may tolerate uptitration faster than in other primary headache disorders
- Often reasonable to wean once attack-free for at least 2 weeks

Cluster Preventive Options: Verapamil

- Typically first-line despite Level C evidence
- 50-94% of patients respond to verapamil
- Start as low as 80 or 120mg daily
- Effective dose range often 240-360mg daily, but patients may respond at lower or higher doses
  - With immediate-release form, divide three times daily
- Side effects: constipation, hypotension, ankle edema, bradycardia, nausea, dizziness, rash
- ECG monitoring required above 360mg daily

Petersen A et al Headache 2019; May A et al Nat Rev Dis Primers 2018; Diener C and May A Drugs 2022.

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Cluster Preventive Options: Other

- Lithium
  - Side effects are common: tremor, nausea, diarrhea, polyuria/polydipsia, hypothyroid
- Topiramate 100-200mg daily
  - Less evidence, side effects may limit – brain fog, paresthesias, weight loss, mood changes
- Melatonin 10-25mg nightly 2-3 hours before bed
  - Less evidence but often better tolerated – sleepiness, vivid dreams
  - Can consider lower dose year-round, escalate during bouts
- Gabapentin 300-1800mg nightly 2-3 hours before bed
  - Even less evidence but may be better tolerated – dizziness, fatigue, weight gain, edema
- Galcanezumab 300mg
  - Only approved for episodic cluster headache
  - Trials in chronic cluster did not meet endpoints, but improvement in quality of life and attack frequency in observational studies

Petersen A et al Headache 2019; May A et al Nat Rev Dis Primers 2018; Diener C and May A Drugs 2022; Goadsby PJ et al. N Engl J Med 2019; Riesenberg R et al. Cephalalgia 2022; Lamas Perez R et al Cephalalgia 2024

Cluster: Psychedelics/Hallucinogens?

- Clusterbusters
- Psilocybin
- LSD
- GHB

Case 1: 50-year-old Female - Revisited

This patient has a history of myocardial infarction and a pacemaker. Which one of the following acute treatments would be a good choice?

A. Sumatriptan subcutaneous
B. Zolmitriptan nasal spray
C. Lidocaine nasal spray
D. Vagus nerve stimulator

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Case 1: 50-year-old Female - Revisited

- Diagnosed with episodic cluster headache
- Acute treatment: high-flow oxygen, lidocaine nasal spray
- Transitional treatment: Suboccipital nerve block with steroid weekly x 2 weeks stopped cluster attacks within first week
- Preventive: Melatonin, no others needed for now

May need to be performed up to 3 times

Vagus nerve stimulator: contraindicated with implantable medical devices, metallic devices near neck, simultaneous use of another device e.g. TENS unit or mobile phone

Case 2: 70-year-old Female

- Referred for “migraine”
- 3-year history of headache
- Constant pain behind left eye
- Exacerbations to severe lasting up to several hours
- She reports left eye tearing and left eye photophobia during exacerbations
- No benefit from amitriptyline or propranolol

Case 2: 70-year-old Female

Which one of the following is the best first treatment option?

A. OnabotulinumtoxinA injections
B. Verapamil
C. Lamotrigine
D. Indomethacin

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Case 2: 70-year-old Female

- Referred for “migraine”
- 3-year history of headache
- Constant pain behind left eye

Side-locked

- Exacerbations to severe lasting up to several hours
- She reports left eye tearing and left eye photophobia during exacerbations

Ipsilateral photophobia

- No benefit from amitriptyline or propranolol

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ICHD-III PH/HC

Unique to PH/HC: prevented by indomethacin

Note: Migrainous features are COMMON in PH/HC and may overshadow autonomic symptoms

Paroxysmal Hemicrania

- **A** **At least 20 attacks fulfilling criteria B–E**
- **B** **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 with a frequency of ≥5 per day**[b]
- **E** **Prevented absolutely by therapeutic doses of indomethacin**
- **F** **Not better accounted for by another *ICHD-3* diagnosis**

Hemicrania Continua

- **A** **Unilateral headache fulfilling criteria B–D**
- **B** **Present for >3 months, with exacerbations of moderate or greater intensity**
- **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, or aggravation of the pain by movement
- **D** **Responds absolutely to therapeutic doses of indomethacin**
- **E** **Not better accounted for by another *ICHD-3* diagnosis**

Burish M. Continuum 2018, modified from ICHD-III, Cephalalgia 2018

PH/HC Treatment

Consider an indomethacin trial in any side-locked headache or uncertain diagnosis

- Start 25mg tid, increase to **75mg tid** over 1-3 weeks, continue for at least **2 weeks**
- Consider trial of wean once in remission
- Consider stomach protection with PPI or H2 blocker

Other options:

- NSAIDs: Celecoxib, piroxicam
- Indomethacin-similar: Melatonin, Boswellia serrata
- General options: Topiramate, verapamil, gabapentin, acetazolamide
- Onabotulinumtoxin injections for HC?
- Nerve blocks?
- Vagus nerve stimulator FDA-cleared in USA for PH/HC

Baraldi C et al. J Headache Pain 2017
Nahas SJ Continuum 2021

Case 2: 70-year-old Female - Revisited

- Diagnosed with hemicrania continua
- Headache resolves completely after indomethacin trial
- Develops gastric ulcer and needs to stop indomethacin
- Switched to melatonin + Boswellia, report mild occasional attacks but overall these are tolerable

Case 3: 40-year-old Male

- Referred for “trigeminal neuralgia”
- 3-year history of headaches
- Shock-like pain behind left eye
- Attacks last 10 seconds to 2 minutes, 80+ times per day
- Left eye redness and tearing during attacks
- Attacks are spontaneous or triggered by touching the left forehead
- Patient is considering medical assistance in dying due to pain

Case 3: 40-year-old Male

- Referred for “trigeminal neuralgia”
- 3-year history of headaches
- Shock-like pain behind left eye
- Attacks last 10 seconds to 2 minutes, 80+ times per day

Short and frequent

- Left eye redness and tearing during attacks
- Attacks are spontaneous or triggered by touching the left forehead
- Patient is considering medical assistance in dying due to pain

ICHD-III SUNCT/SUNA

Short-lasting unilateral neuralgiform headache attacks

A At least 20 attacks fulfilling criteria B-D

B Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or othe trigeminal distribution, lasting for 1-600 seconds and occurring as single stabs, series of stabs, or in a sawtooth pattern

C At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain

1 Conjunctival injection and/or lacrimation

2 Nasal congestion and/or rhinorrhea

3 Eyelid edema

4 Forehead and facial sweating

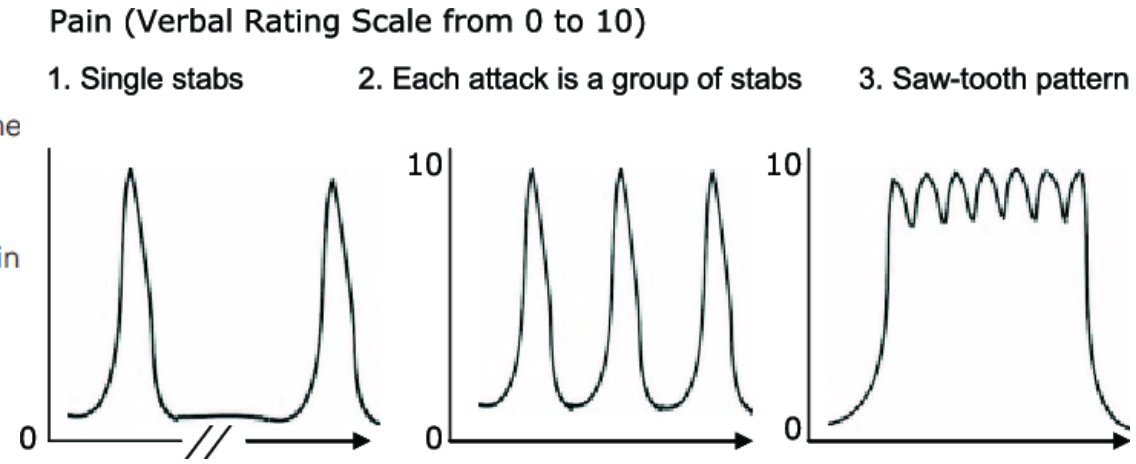
5 Forehead and facial flushing

6 Sensation of fullness in the ear

7 Miosis and/or ptosis

D Occurring with a frequency of at least one a day[b]

E Not better accounted for by another *ICHD-3* diagnosis



- Prominent tactile triggers
- Usually no refractory period, unlike trigeminal neuralgia
- Can still have restlessness

SUNCT: both conjunctival injection AND tearing
SUNA: either conjunctival injection OR tearing

Burish. Continuum 2024
Cohen A et al. Brain 2006

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SUNCT/SUNA Treatment

- **Lamotrigine 100-400mg daily**
- Lidocaine iv or mexiletine oral
- Others: topiramate, gabapentin, carbamazepine, duloxetine
- Weak evidence for occipital nerve blocks, onabotulinumtoxinA injections
- **Trial of indomethacin in case missed PH or other indomethacin-responsive headache** - sawtooth pattern of pain may make determining attack length difficult

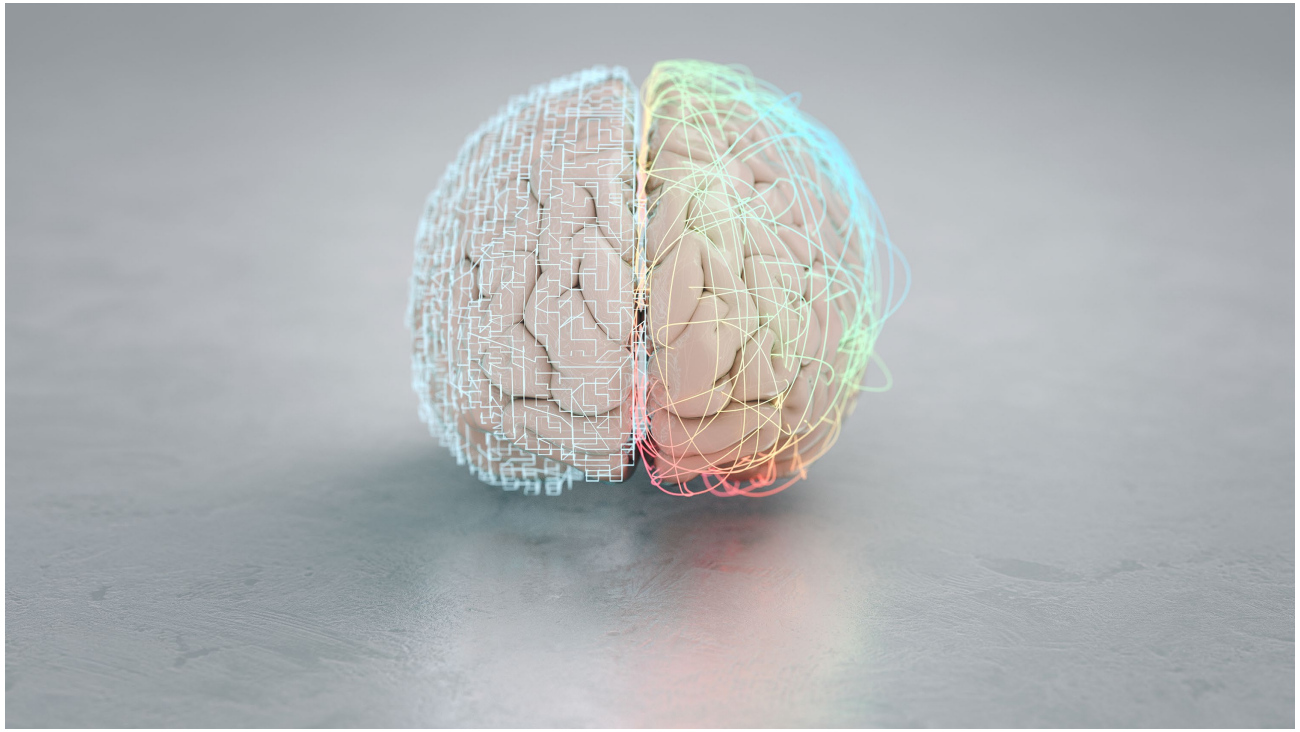
Cohen A et al. Brain 2006; Levy and Matharu Ann Indian Acad Neurol 2018; Miller S. et al. Brain 2016; Miller and Matharu Curr Pain Headache Rep 2014; Nahas SJ Continuum 2021; Weng H-Y. et al. Cephalalgia 2018

Case 3: 40-year-old Male - Revisited

- Diagnosed with SUNCT
- Started on lamotrigine
- Attacks decrease to 10-20 per day and are less intense

Differentiating TACs

- Duration
- Attack frequency
- Associated features
- Triggers
- Treatment response



Nahas SJ. Continuum 2021

TACs: Take-Home Points

- TACs are severe, unilateral headaches with one or multiple ipsilateral trigeminal autonomic features
- Attack duration may be helpful in distinguishing between TACs
- All patients should be investigated for secondary causes
- Consider indomethacin trial even if story is not classic for PH/HC

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THANK YOU

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