Trigeminal Autonomic Cephalalgias

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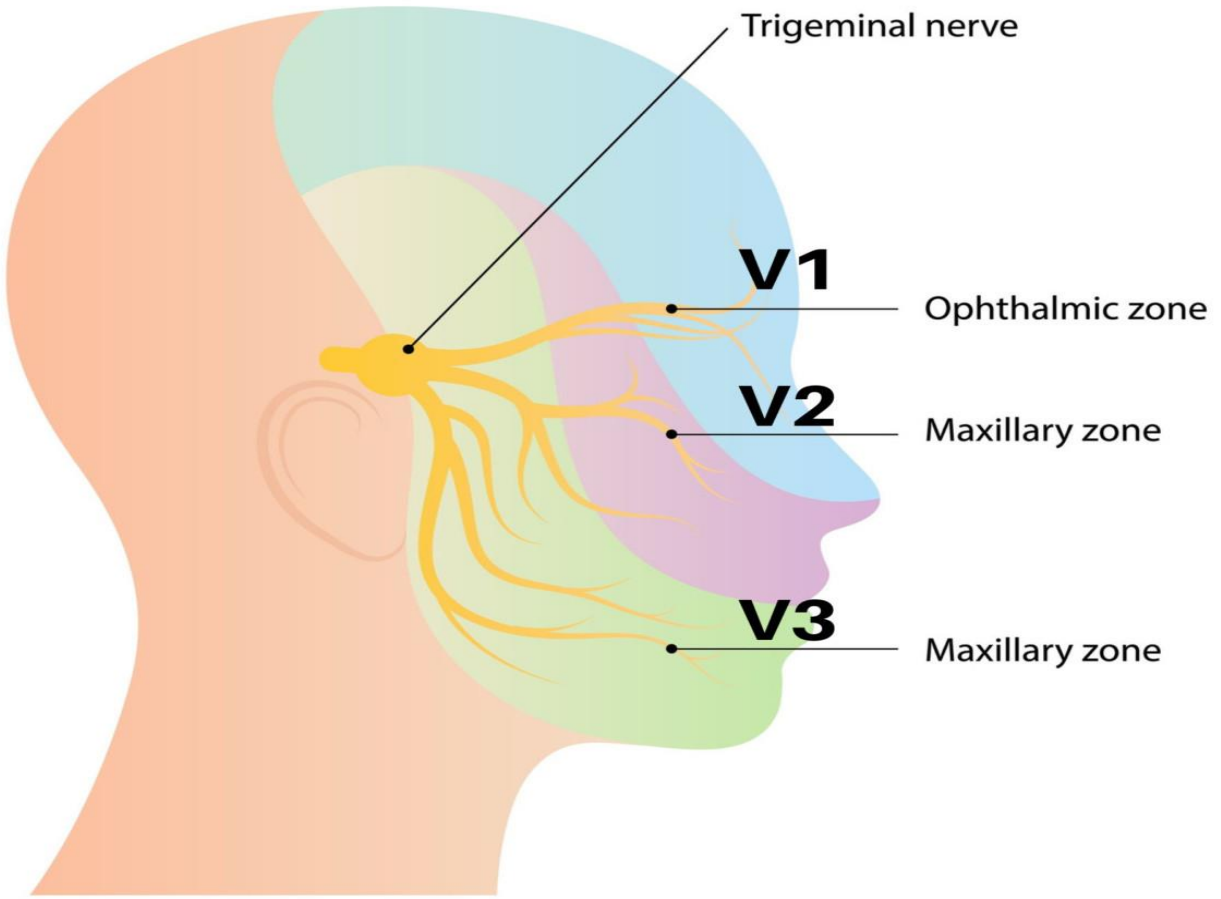
Introduction

IMPORTANCE Trigeminal autonomic cephalalgias (TACs) comprise a unique collection of primary headache disorders characterized by moderate or severe unilateral pain, localized in in the area of distribution of the first branch of the trigeminal nerve, accompanied by cranial autonomic symptoms and signs. Most TACs are rare diseases, which hampers the possibility of performing randomized clinical trials and large studies. Therefore, knowledge of treatment efficacy must be based only on observational studies, rare disease registries, and case reports, where real-world data and evidence play an important role in health care decisions.



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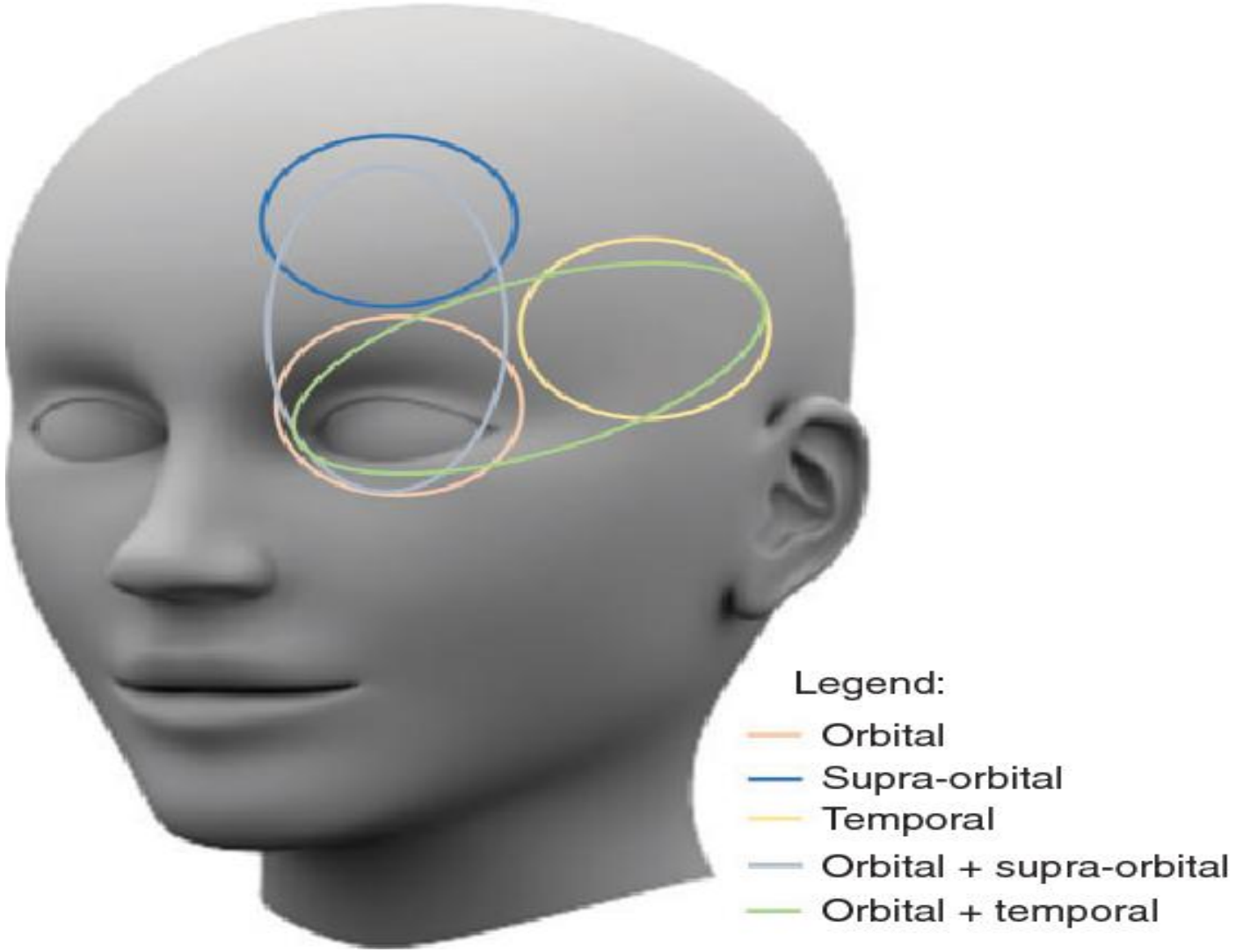

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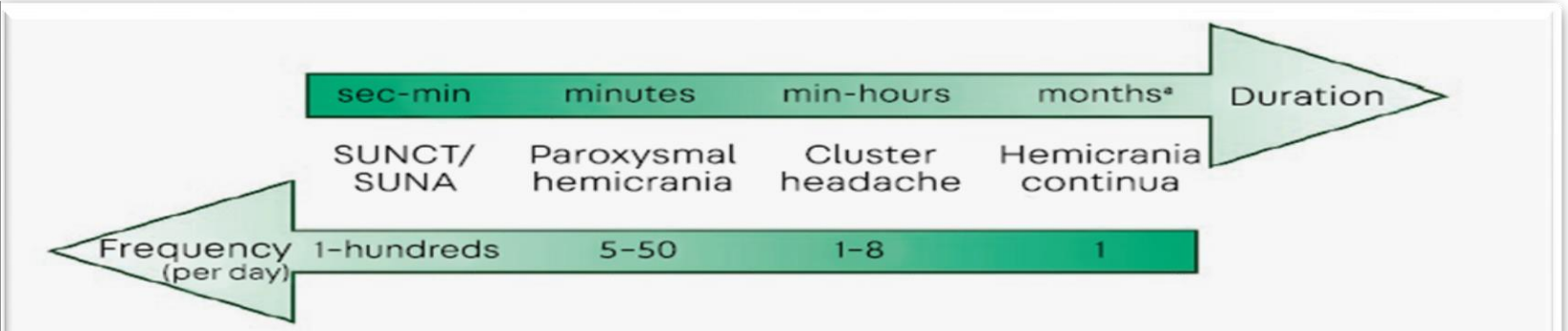
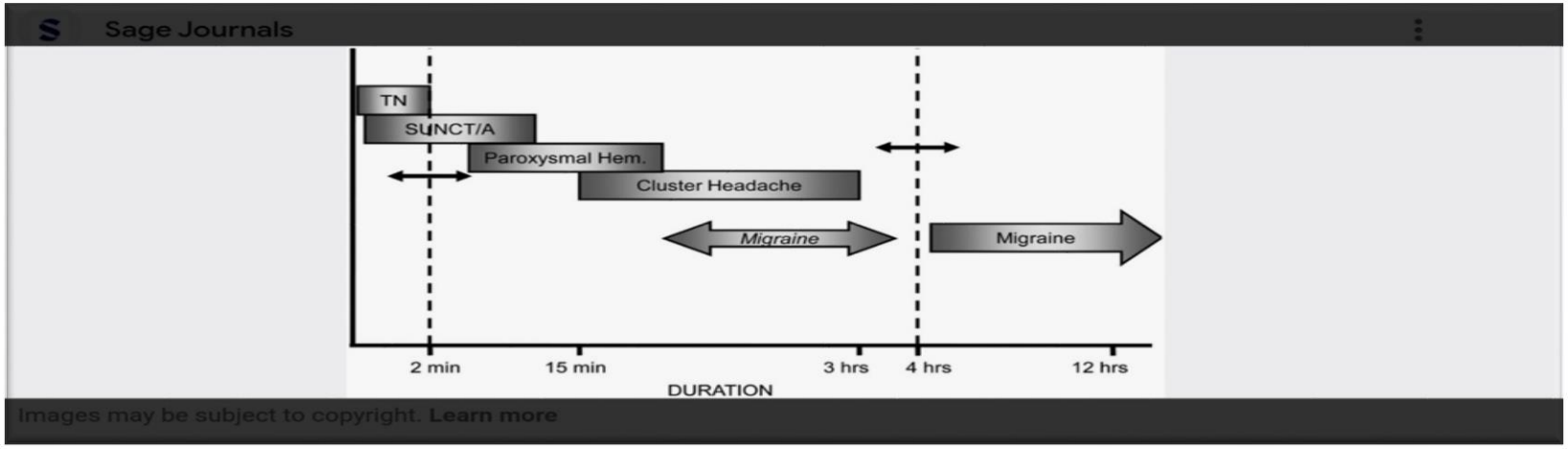


FIGURE 9-1
Timing of individual attacks in trigeminal autonomic cephalalgias. Listed are typical durations of individual attacks and frequencies of attacks per day. Considerable overlap exists between the disorders. Of note, the frequency of cluster headache is officially between one attack every other day and eight per day.[6]

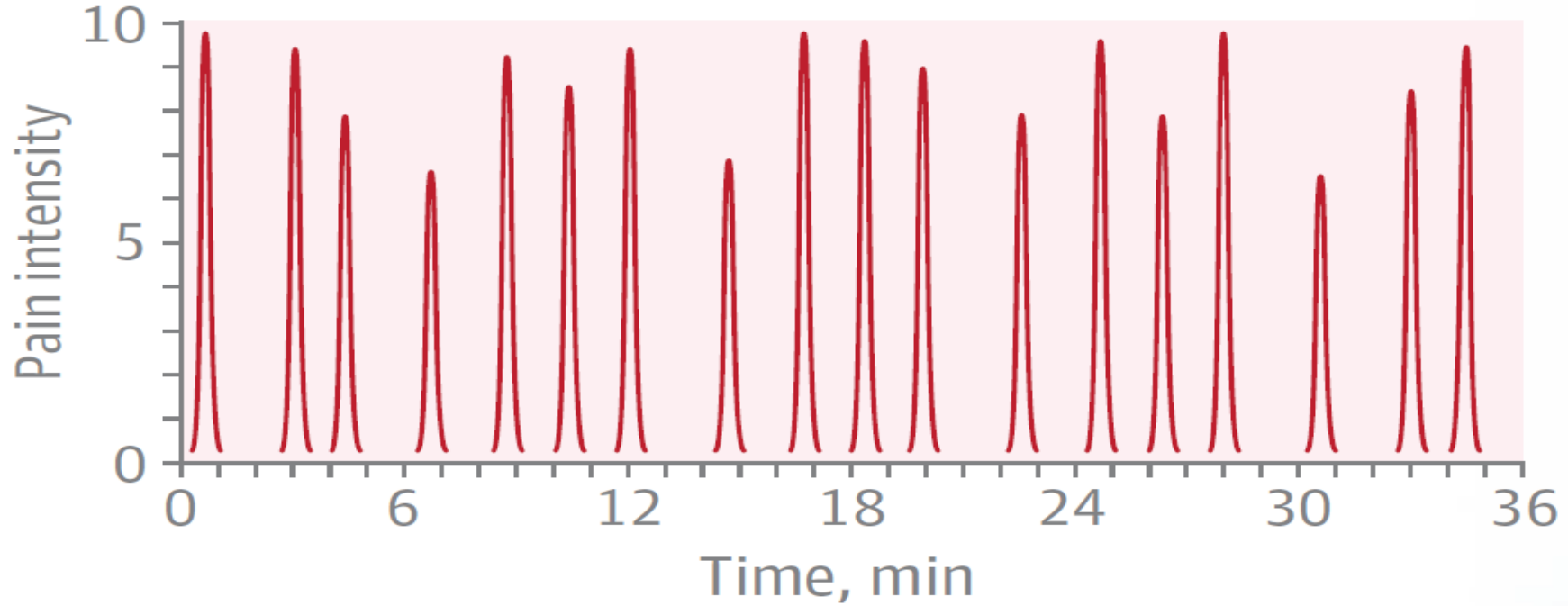
SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.
[a] While a hemicrania continua headache lasts months, flares in hemicrania continua pain can last minutes to days.



SUNCT/SUNA

Duration: 5-600 s (usually 10-120 s; mean, 60 s)

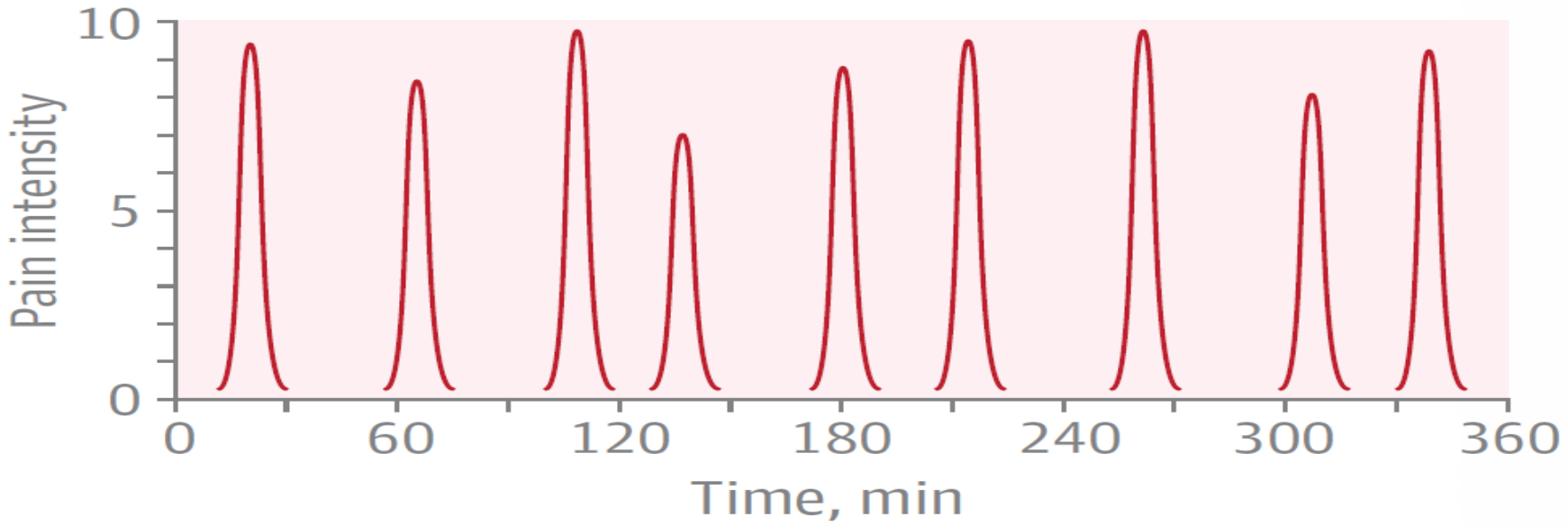
Frequency: 3-200 per day (mean, 28 per day)

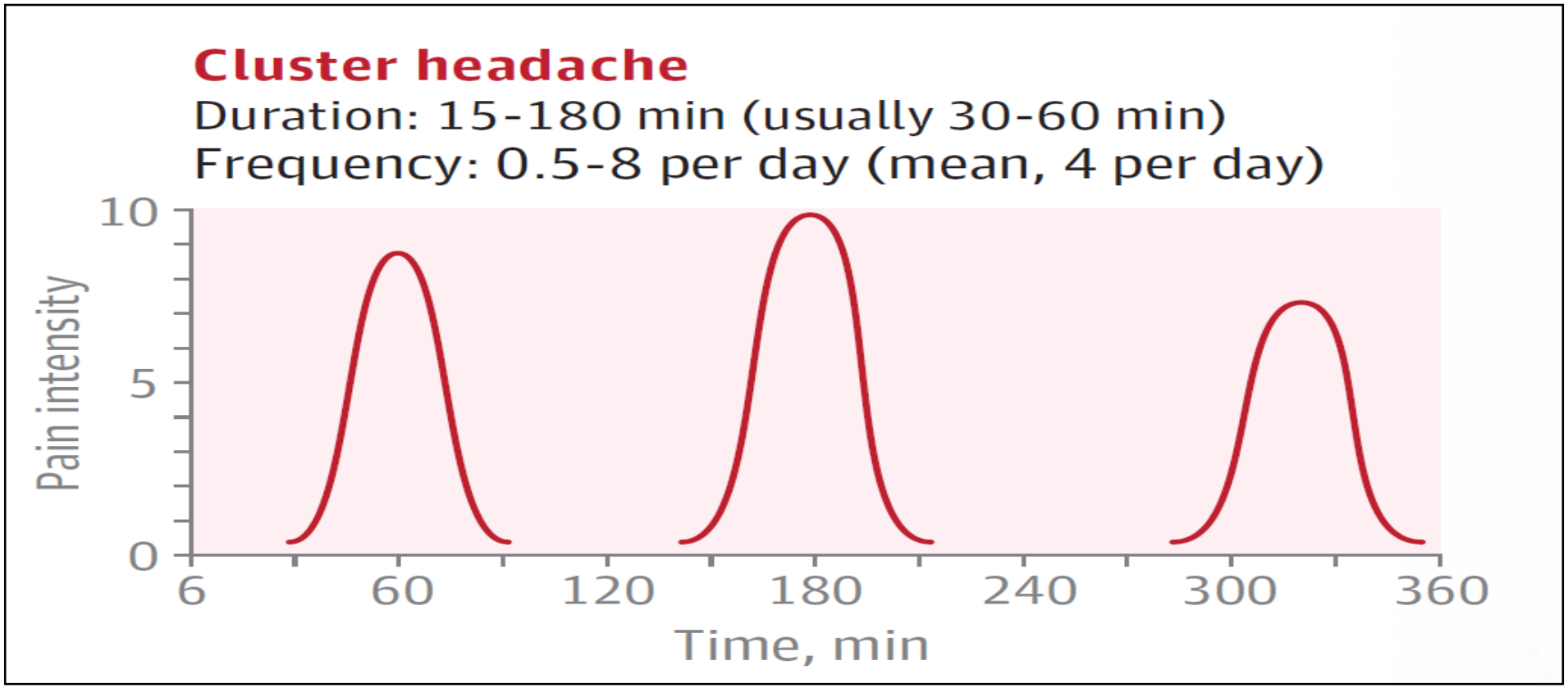


Paroxysmal hemicrania

Duration: 2-30 min (mean, 26 min)

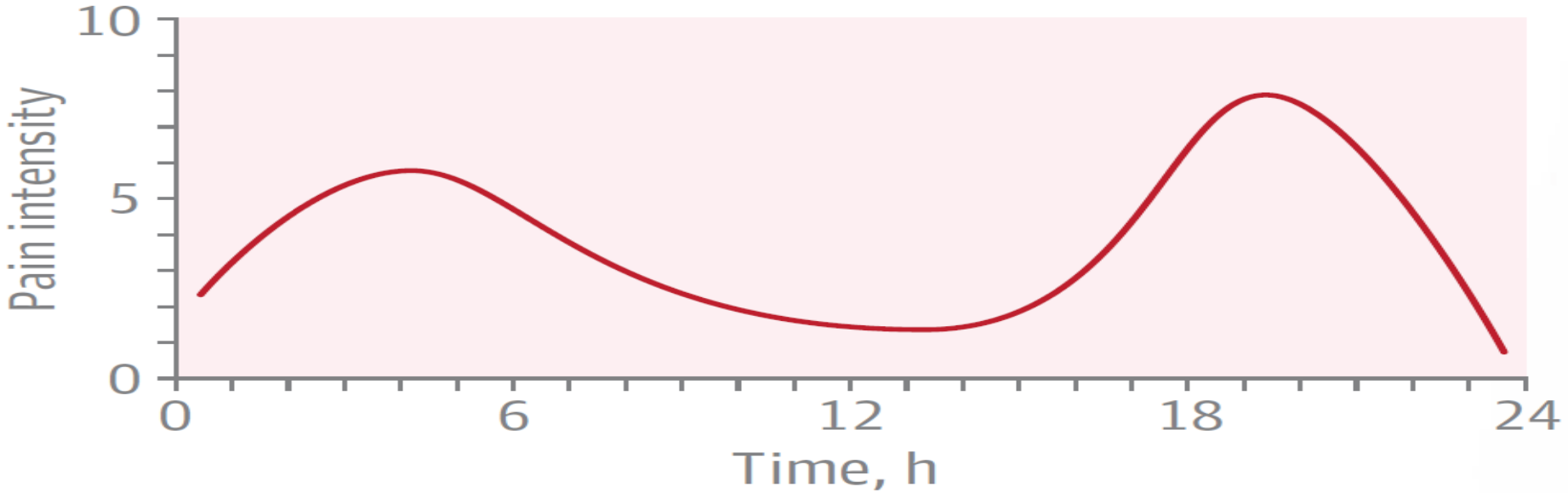
Frequency: 5-40 per day (mean, 15 per day)

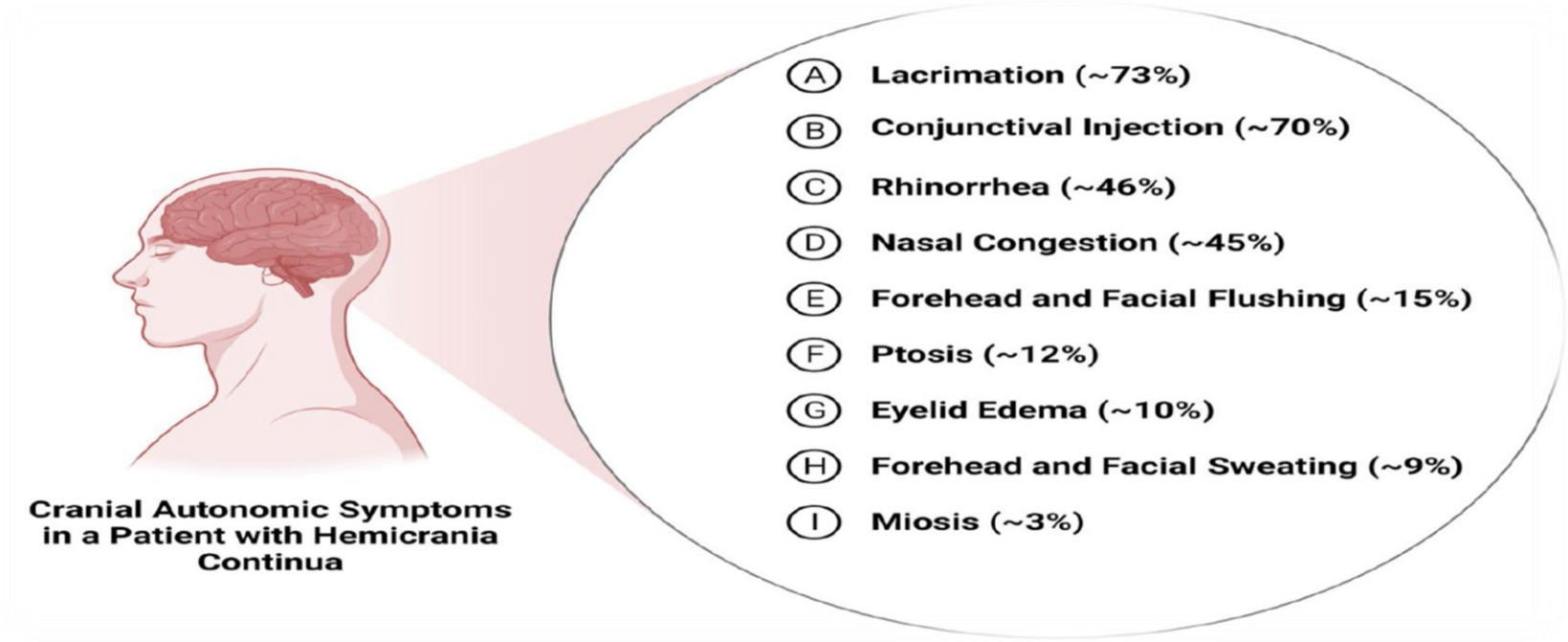


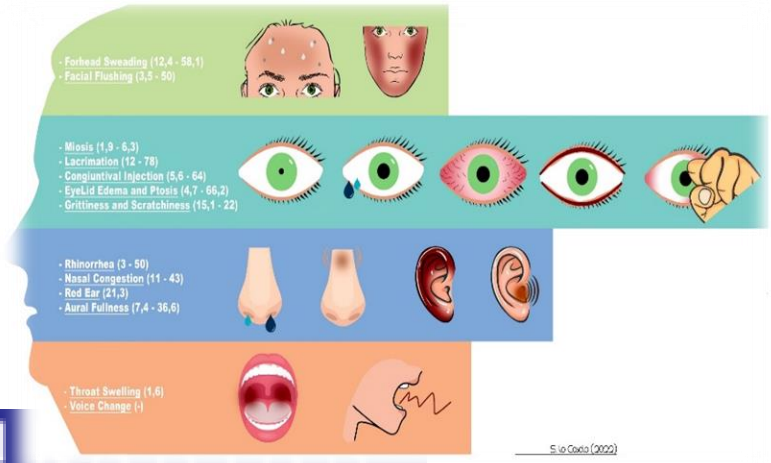


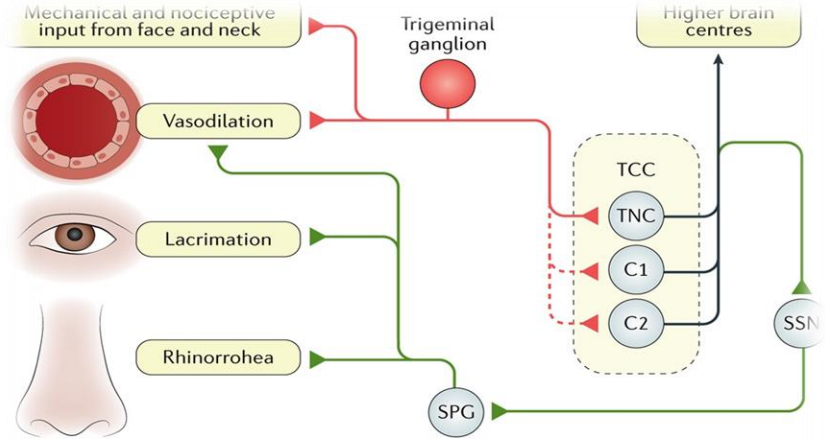
Hemicrania continua

Continuous pain with exacerbations









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ICHD-3 Diagnostic Criteria for Cluster Headache[a]

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)[b]

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[c]

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

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

[a] Reprinted with permission from Headache Classification Committee of the International Headache Society, Cephalalgia.[1] © 2018 International Headache Society.

[b] During part, but less than half, of the active time-course of cluster headache, attacks may be less severe and/or of shorter or longer duration.

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

TABLE 5-5

ICHD-3 Diagnostic Criteria for Paroxysmal Hemicrania[a]

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[c]

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

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

[c] In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.

TABLE 5-6

ICHD-3 Diagnostic Criteria for Short-Lasting Unilateral Neuralgiform Headache Attacks[a]

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 other 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

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[b] During part, but less than half, of the active time-course of short-lasting unilateral neuralgiform headache attacks, attacks may be less frequent.

TABLE 5-7

ICHD-3 Diagnostic Criteria for Hemicrania Continua[a]

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[b]

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

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

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[b] In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.

TABLE 5-3

Some Secondary Causes or Mimics of Trigeminal Autonomic Cephalalgias

Vascular

- Cervical arterial dissection
- Intracavernous carotid artery thrombosis
- Carotid-cavernous sinus fistula
- Cerebral venous or cavernous sinus thrombosis
- Subclavian steal
- Lateral medullary infarction

Nonvascular

- Glaucoma
- Sinusitis (especially sphenoid)
- Trigeminal nerve root compression
- Cavernous sinus metastasis
- Giant meningioma
- Pituitary tumor
- Clival epidermoid
- Idiopathic intracranial hypertension

TABLE 5-1 **Clinical Characteristics That Help to Distinguish Trigeminal Autonomic Cephalalgias and Other Primary Headache Syndromes**

Syndrome	Pain location	Attack duration	Autonomic features	Migrainous features	Exacerbants
Trigeminal autonomic cephalalgias					
Cluster	Unilateral frontal/temporal/periorbital	Minutes to hours	Always	Sometimes	Alcohol, sleep
Paroxysmal hemicrania	Unilateral frontal/temporal/periorbital	Minutes	Always	Sometimes	Neck turning
Short-lasting unilateral neuralgiform headache attack syndromes (SUNHA)	Unilateral V1	Seconds to minutes	Always	Rarely	Cutaneous, thermal, mechanical
Hemicrania continua	Unilateral	Minutes or hours superimposed on baseline pain	Always	Often	Variable

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TABLE 5-8

Clinical Characteristics Distinguishing the Trigeminal Autonomic Cephalalgias and First-line Therapies Used for Them

Disease	Attack duration	Attack frequency	Sex ratio (F:M)	Acute treatment	Preventive/bridge treatment
Cluster headache	15-180 min	Every other day to eight per day	1:2 to 1:7 (older studies show greater male predominance)	Oxygen, subcutaneous sumatriptan, nasal spray sumatriptan or zolmitriptan, noninvasive vagus nerve stimulation	Suboccipital steroid injection, oral prednisone taper, verapamil, lithium, galcanezumab, noninvasive vagus nerve stimulation
Paroxysmal hemicrania	2-30 min	1-40 per day	2:1 to 3:1	N/A (attacks too short)	Indomethacin
Short-lasting unilateral neuralgiform headache attack syndromes (SUNHA)	1-600 sec	Dozens to hundreds per day	1:1.5	N/A (attacks too short)	Lamotrigine, topiramate, gabapentin, indomethacin (in some patients)
Hemicrania continua	Continuous pain with superimposed attacks lasting minutes to days	Up to dozens per day	2:1	N/A (superimposed exacerbations too short)	Indomethacin

N/A = not applicable.

TABLE 5-4

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

	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]

Current avaliable treatment options for cluster headache

ACUTE TREATMENT

Subcutanous injection of sumatriptan
Sumatriptan and zolmitriptan nasal spray

Inhaled 100% oxygen 12-15 L/min

TRANSITIONAL TREATMENT

Block of the Great Occipital Nerve (GON)
(betametasone and lidocain with adrenalin)

Prednisone 75-100 mg for 5 days
(followed by a slow trapering off)

PREVENTIVE TREATMENT

First-line
Verapamil 360-960 mg
(ECG monitoring)

Second-line
Lithium
(se-lihtium: 0.5-0.8 mmol/L)

Topiramate 50-200 mg

Table 1 Comparison of triptans in acute cluster headache treatment

Triptan	Efficacy	Cost (as per BNF April 2019)
Subcutaneous sumatriptan 6 mg	Headache relief rates at 15 min: placebo 26% and sumatriptan injection 74%[19]	Imigran £50.96 for two injections Generic £39.50 for two injections
Sumatriptan nasal spray 20 mg	Pain-free rates at 30 min: placebo 18% and sumatriptan nasal spray 47%[24]	Imigran £14.16 for two or £42.47 for six
Zolmitriptan nasal spray 5 mg and 10 mg	Headache relief rates at 30 min (defined as reduction in pain severity): placebo 21%; zolmitriptan nasal spray 5 mg 40% and zolmitriptan nasal spray 10 mg 62%[23]	Zomig 5 mg/0.1 mL nasal spray 0.1 mL unit dose- £36.50 for six 10 mg formulation—not available.

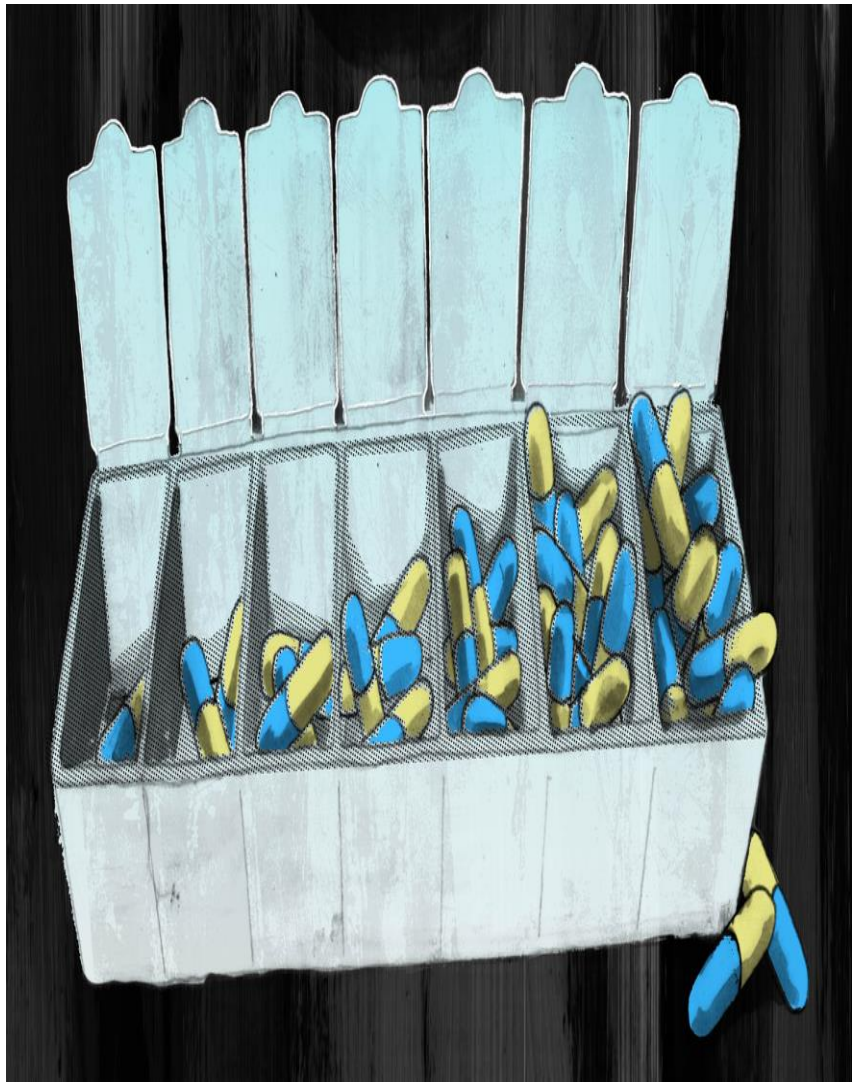


Table 2 Recommended verapamil titration regimen[34]

	Morning	Midday	Evening
For 2 weeks take:	80 mg	80 mg	80 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	80 mg	80 mg	160 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	80 mg	160 mg	160 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	160 mg	160 mg	160 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	160 mg	160 mg	240 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	160 mg	240 mg	240 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	240 mg	240 mg	240 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	240 mg	240 mg	320 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	240 mg	320 mg	320 mg
Arrange an ECG: if normal then:			
For 2 weeks take:	320 mg	320 mg	320 mg

Table 5 Three-tier algorithm of oral preventive treatments for short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms

	Medications (maximum dose)
First-line treatment	▶ Lamotrigine (up to 700 mg/day)
Second-line treatments	▶ Oxcarbazepine (up to 2400 mg/day) ▶ Duloxetine (up to 120 mg/day) ▶ Carbamazepine (up to 1600 mg/day) ▶ Topiramate (up to 800 mg/day)
Third-line treatments	▶ Gabapentin (up to 4800 mg/day) ▶ Pregabalin (up to 600 mg/day) ▶ Lacosamide (up to 400 mg/day) ▶ Mexiletine (up to 1200 mg/day)

Cranial neuropathies

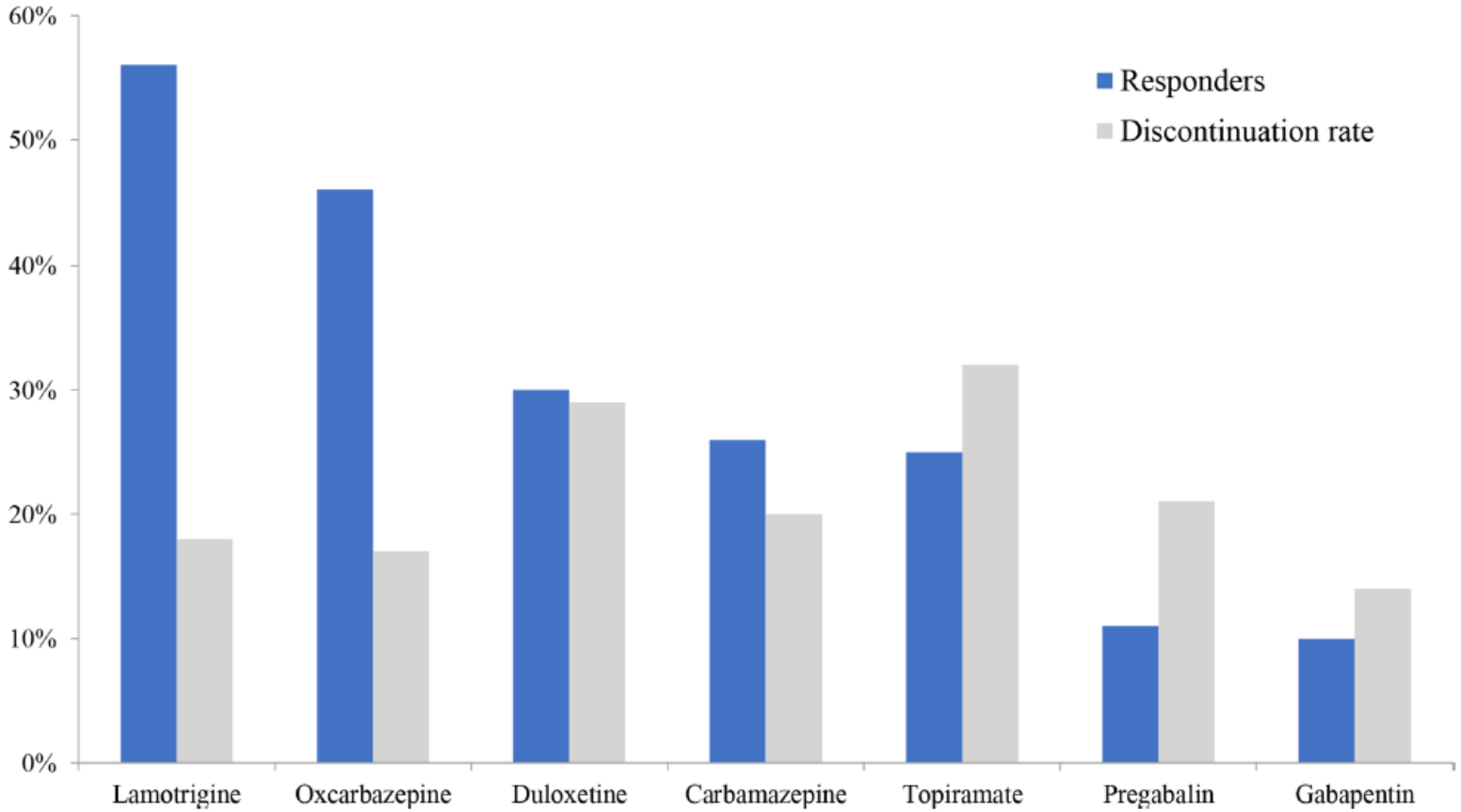
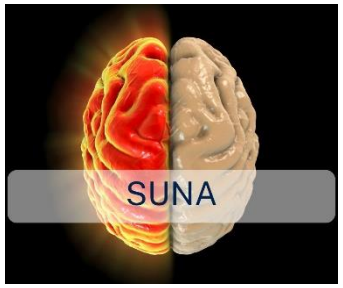
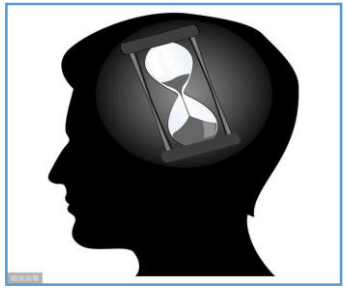
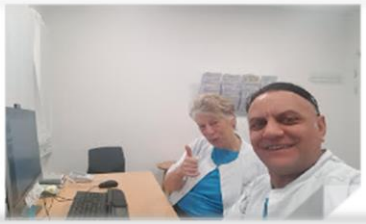


Figure 1 Responder and discontinuation rates secondary to adverse effects for oral medical treatments in SUNCT and SUNA. SUNCT: Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injections and Tearing; SUNA: Short-lasting Unilateral Neuralgiform headache attacks with autonomic symptoms. * Mexiletine and lacosamide data were not included due to small sample size.







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