Primary Headache Disorders

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KEYWORDS

• Migraine • Tension-type headaches • Trigeminal autonomic cephalgias
• Hemicrania continua

KEY POINTS

- Primary headache disorders include migraine, tension-type headaches, and the trigeminal autonomic cephalgias (TACs).
- "Primary" refers to a lack of clear underlying causative pathology, trauma, or systemic disease.
- The TACs include cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting neuralgiform headache attacks with conjunctival injection and tearing (SUNCT); hemicrania continua (HC), although classified separately by the International Headache Society (IHS), shares many features with both migraine and the TACs.
- The IHS classification system is viewable at http://ihs-classification.org/en/.

INTRODUCTION

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MIGRAINE

Migraine is a common primary headache with an additional number of rarer related syndromes.[1] Prevalence studies in Western countries show that migraine affects approximately 10% to 12% of the adult population, but figures are not always

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consistent.[2–5] The 2 most common types of migraine headaches are migraine without aura (MWA) and migraine with aura (MA).[6] The combination of a high prevalence, severe pain, and debilitating neurologic symptoms results in a substantial social impact with decreased quality of life.[7,8]

MWA is an inherited disorder affecting the young, with an onset before the age of 20 years in about half of the cases.[9] There is up to a twofold increase of MWA among first-degree relatives of patients with MWA and a fourfold increase in MA.[10,11] Studies suggest that multiple receptor polymorphisms and multigene inheritance are involved.[12,13]

Migraine presentation may be divided into phases and each may occur alone or in combination with each other. The headache phase is identical in MA and MWA.

- Prodrome
  - Premonitory signs and symptoms occurring days or hours before some or all headaches.[14,15]
  - Nonspecific neurologic/autonomic signs and constitutional symptoms. Tiredness, difficulty in concentration, and stiff neck.
- Aura (in MA)
  - Focal neurologic signs or symptoms: Visual (flashing lights), sensory (pins and needles), and motor (speech) symptoms.
  - Develop over 5 to 20 minutes and last for less than 60 minutes.
  - Followed in about 10 minutes by a typical headache.[16]
- Headache phase
  - See summary later in this article.
- Postdrome
  - Depressed, irritable, and tired.

Migraine Without Aura

Most common form of migraine.[1]

Summary of features of the headache phase

- Typically unilateral; no side preference.
  - Side-locked migraine in up to half of migraineurs.[17]
  - Bilateral in some patients.[17–19]
- Usually ocular, temporal, and frontal regions.[17]
  - Also occipital and neck regions.[17]
- Throbbing or pulsating; occasionally pressing.[19–21]
- Moderate to severe intensity.[9]
  - Not uniform.[21]
- Sharp periorbital "ice-pick" pains[22] interictally.
- Routine physical activity aggravates pain.[19,20]
  - Moving the head or coughing will accentuate headaches.
- Headache is insidious, may take 0.5 to 2.0 hours.[23]
- Periodic, typically lasting 4 to 72 hours.[1]
- Frequency is, in most cases, less than 1 per month[9,24,25] but may vary from up to 2 to 12 headaches per month.
- Vast majority report nausea and photophobia or phonophobia.[18,19]
  - 50% vomit during an attack.
- Autonomic signs (AS)
  - Usually lacrimation (≈50%), linked to severity.[26,27]

Migraine Triggers

Several factors have been reported as initiators of individual attacks in migraineurs, termed triggers or precipitating factors,[28] and are reported by up to 90% of migraineurs[29,30]:

- Anxiety and stress.[30,31]
- Fatigue, sleeping difficulties.
  - Occasionally woken from sleep by a migraine,[32] early morning.[33]
  - Interestingly, sleeping may abolish headache.[32]
- Foods and drinks.
- Menstruation.
  - Hormone variations[34] associated with migraine onset and patterns.
  - A quarter of women report menstrually related migraine,[35,36] more so in clinic-based populations.[29,37,38]
  - Improvement or resolution of migraine headaches during late pregnancy.[20,39]
- Weather changes.
- Smells, smoke, and light.[40]

Differential Diagnosis

- Tension-type headache (TTH)
  - Clinical overlap with mild MWA is prominent.[41]
- Oral/Dental
  - Neurovascular pain in the lower face/oral cavity reported.[42,43]
    - Termed facial migraine, lower-half facial migraine or neurovascular orofacial pain.[42–45]
- Sinusitis
  - Extremely common misdiagnosis, particularly in migraines with midface pain.[46,47]
- Vascular disorders
  - Transient ischemic attacks, thromboembolic stroke, intracranial hematoma, subarachnoid hemorrhage, and arterial hypertension may cause migrainelike headaches.[48]
- Intracranial tumors, infections and regional trauma may induce migrainelike headaches.
- Some are sudden-onset headaches or are accompanied by atypical neurologic signs and symptoms.
  - See indications for neuroimaging in headaches.[49,50]
- Cervicogenic headache may clinically resemble migraine.

Chronic Migraine

Some migraine sufferers may have a clinically progressive disease in which migraine episodes increase in frequency over time.[51,52] A proportion of migraineurs (15.6%) describe daily or near-daily headaches[21] and approximately 2.5% of the general population has chronic migraine (CM). MWA is most prone to accelerate with frequent use of symptomatic medication, resulting in medication-overuse headache.[1] However, limited data are at our disposal to predict which patients will progress from episodic to CM.[52] The risk increases significantly in whites, with obesity and a high baseline headache frequency.[53,54]

Summary of CM features

- Bilateral; frontotemporal region.
  - Up to half may be strictly unilateral.[55,56]

- Mostly mild to moderate.
- Dull, pressing quality.[55]
- Occurs more than15 days per month (>3 months) with no medication overuse.[1]
  - Truly continuous headache in fewer than half of patients.
    - Superimposed, severe typical migraine attacks occur.[55,56]
- Nighttime arousals due to headache reported, particularly by women.[55,56]
- Most cases seem to begin as episodic migraine and transform.[57,58]
  - Many patients report episodic migraine that at approximately age 30 to 40 became increasingly frequent.
- Particularly in women, CM is still accompanied by mild migrainous features.[55,59]
- Menstrual relation and other triggers may still be prominent.[55,59]

Anxiety and depression seem to be common in patients with CM, affecting from one-third to nearly 90% of patients.[55] Hypothalamic dysfunction has been found in CM.[60]

Migraine Comorbidity

Strong evidence suggests a relation between migraine and depression or anxiety, stroke (particularly in MA with smoking), other pain syndromes, and allergies.[61,62]

Pathophysiology

Migraine is considered to be a result of a primary brain dysfunction, particularly in brainstem structures, that leads to activation and sensitization of the trigeminovascular system. The detailed pathophysiology of migraine is beyond the scope of this article. The reader is referred to pertinent reviews.[63,64]

Migraine Treatment

Although there is no cure, adequate control can be achieved for most migraineurs.

Nonpharmacologic treatment

- Patient education
  - Accurate, comprehensible information on importance of contributing factors, such as sleep, diet, and other lifestyle practices that may precipitate attacks.[65]

Pharmacologic treatment

- Abortive (acute, symptomatic).
  - Aim to rapidly relieve headache with no recurrence or side effects.
  - Used when fewer than 4 to 8 attacks per month or to supplement prophylactic regimens.
  - Nonspecific medication (**Table 1**).
    - Complementary treatments, such as butterbur, feverfew, and coenzyme-Q, may also be effective.[66]
  - Triptans (see **Table 1**)
    - Triptans of choice.[67]
      - Rizatriptan 10 mg consistently provides rapid relief.[67,68]
      - Almotriptan (12.5 mg) has good efficacy and tolerability.
      - Eletriptan will provide high efficacy with low recurrence but low tolerability.[68]
      - Frovatriptan for the prevention of menstrually related migraine.[69–71]

Table 1
Some of the common abortive treatments for migraine

Class	Drugs	Initial Oral Dose, mg
Analgesics	Aspirin	500–1000
Combinations	Aspirin and	500–600
	Paracetamol and	200–400
	Caffeine	50–200
	Paracetamol and	400
	Codeine	25
Ergot alkaloids	Dihydroergotamine NS	2
NSAIDs:		
Nonspecific	Naproxen sodium	550–825
	Ibuprofen	400–800
	Diclofenac	50–100
Selective COX 2 inhibitors	Rofecoxib	25–50
Triptans (5HT agonist)	Sumatriptan	50–100
	Sumatriptan NS	20 (1 NS metered dose)
	Sumatriptan SC	6
	Naratriptan	2.5
	Eletriptan	40
	Rizatriptan	10
	Zolmitriptan	2.5
	Zolmitriptan NS	2.5 (1 NS metered dose)
	Frovatriptan[a]	2.5
Opioids	Butorphanol NS	1–2 metered doses

Abbreviations: NS, nasal spray; NSAIDs, nonsteroidal anti inflammatory drugs; SC, subcutaneous injection.

[a] Schedule to prevent menstrually related migraines: 2.5 mg for 6 days during the perimenstrual period, loading dose of 2–4 tablets on day 1, followed by twice-daily frovatriptan 2.5 mg.

- Preventive (chronic, prophylactic; **Table 2**).
  - Aims to reduce attack frequency, severity, and duration.[72]
  - Use in frequent (>4–8 attacks monthly) or debilitating attacks.[72,73]
    - Early and aggressive treatment of frequent migraine is indicated.[74,75]
  - Drugs with high efficacy and mild to moderate adverse events.
    - β-blockers.
    - Amitriptyline.
    - Divalproex (good in CM).
    - Topiramate.[70,72,76]
    - Choice influenced by medical contraindications or comorbidities, such as insomnia, depression, and hypertension.[77]
  - Drugs with lower efficacy and mild to moderate adverse events.
    - Selective serotonin reuptake inhibitors, calcium channel antagonists, gabapentin, riboflavin, and nonsteroidal anti-inflammatory drugs (NSAIDs).[77]

Treatment Outcome

- About two-thirds of patients will experience a 50% reduction in headache frequency on most preventive therapies.[78]
  - Better rate for sodium valproate.[79]

In summary, migraine is a debilitating syndrome that in mild or atypical forms is often misdiagnosed. Correct diagnosis allows the control of most headaches.

Table 2
Choice of migraine preventive treatment

Drug	Dose, mg	Adverse Events	Contraindications	Relative Indications
Propranolol (SR)	80–240	Bradycardia Hypotension Fatigue Sleep disturbances Dyspepsia Depression	Asthma Depression Cardiac failure Raynaud disease Diabetes	Hypertension Angina
Amitriptyline	10–50	Sedation Weight gain Dry mouth Blurred vision Constipation Urinary retention Postural hypotension	Mania Urinary retention Heart block	Insomnia Anxiety Depression TTH Other chronic pains
Sodium valproate	500–1000	Nausea, vomiting Alopecia Tremor Weight gain/loss	Liver disease Bleeding disorder	Mania Epilepsy Anxiety
Topiramate	25–200	Dizziness, confusion, language problems, paresthesias, nausea, anorexia, diplopia	Renal disease, Respiratory disorders Glaucoma	Overweight

The 4 most effective or commonly used drugs are presented. Choice is influenced by adverse events, comorbidity, and relative indications. The efficacy of all 4 drugs is similar.
Abbreviation: TTH, tension-type headache.

TACS

TACs are primary headaches with a common clinical phenotype consisting of trigeminal pain and AS.

Pathophysiology of TACS

The current pathophysiologic model attempts to explain the 3 major features of the TACs: trigeminal pain, rhythmicity (particularly in CH), and autonomic signs. Taken together, current data suggest that CH and other TACs are conditions whose pathophysiological basis is in the central nervous system, including the hypothalamus, which drives the initiation of the clinical phenotype. Detailed description of the pathophysiology is beyond the scope of this article; see Refs.[80–82]

CH

CH is the archetypal TAC, with severe pain and major autonomic activation.[1] The precise genetics of CH are unclear. However, first-degree relatives of patients with CH are up to 14 to 48 times and second-degree relatives are 2 to 8 times more likely to have CH than the general population.[82] CH is likely to have an autosomal dominant gene with low penetrance.[82]

CH typically appears between the ages of 20 and 29 years[83] and is more common than previously thought: 53 cases per 100,000[84] but may reach 120 to 300 per 100,000[85] and seems to affect men more than women.

A unique feature of episodic CH is the distinctive circadian and circannual periodicity. Episodic CH commonly occurs at least once daily for a period of weeks, at the

same time of day or night.[83] Active periods (6–12 weeks) are followed by a temporary remission that may last from weeks to years (average 12 months). Attacks tend to be shorter and less severe at the beginning and toward the end of each cluster period. At its initial onset, CH active periods are seasonal, occurring around spring or autumn.[86]

There are 2 distinct temporal presentations of CH; most (80%–85%) suffer from the episodic type, characterized by at least 2 cluster periods separated by pain-free periods of 1 month or more over 7 to 365 days.[1] In chronic CH, repeated attacks recur over more than a year without remission or with remission periods lasting less than 1 month. Interictal pain may also be present between attacks or between clusters.[87] Of the 15% of patients with chronic CH, in two-thirds it usually begins as such and in the remaining evolves from the episodic form. Up to half of patients with chronic CH report transition to an episodic pattern.[88] Over the course of the disease, attack duration tends to lengthen in both episodic and chronic CH.

Surprisingly for such a dramatic syndrome, the interval until final diagnosis was 3 to 6 years: 34% to 45% had consulted a dentist and 27% to 33% had consulted an otolaryngologist before accurate diagnosis.[87,89–92] Among factors that increased the diagnostic delay were referral patterns, the presence of migrainous features, an episodic attack pattern, and a young age at onset.

Summary of CH features

The IHS requires at least 5 attacks that meet the criteria outlined.

- Periorbital or ocular[86] pain.
  - "Lower" and "upper" subtypes of CH:
    - Upper CH: forehead, temporal, and parietal regions.[93]
    - Lower CH: temporal, and suboccipital with radiation to the teeth, jaws, neck,[93] teeth, and cheeks.[87,94]
- Unilateral.
  - 20% of cases may change sides.[86]
  - Attacks alternate sides; more common between clusters than between attacks in the same cluster.[86]
- Excruciating severity.
  - Rated as 8 to 10 on a 10-point visual analog scale (VAS) by more than 85% of patients and some report considering suicide.[86]
- Pain is nonspecific: throbbing or boring, burning, stabbing.[95]
  - "Hot poker" or a "stabbing" feeling in the eye.[94]
  - Sudden jabs of intense pain often felt.
- Accompanied by at least 1 of the following ipsilateral autonomic signs:
  - Conjunctival injection/lacrimation
  - Nasal congestion/rhinorrhea
  - Eyelid edema
  - Forehead/facial sweating
  - Miosis and ptosis
  - Restlessness (not a local autonomic sign but frequent [>80%]).
    - Patients appear agitated, continually move around, particularly during severe attacks[96]; in sharp contrast to the quiet-seeking behavior observed in migraine.
- Lasts 15 to 180 minutes
  - Peak intensity is usually rapid: within 3 minutes but may take 9 to 10 minutes.[95]
  - Long-lasting attacks are rare, but may last from 3 to 48 hours.[87]
- Frequency of 1 every other day to 8 per day.

Additional features

- Nocturnal CH is high particularly prevalent (51%–73%).
  - Pain awakens patients within 90 minutes; the onset of rapid eye movement (REM) sleep.[94]
    - Association between episodic chronic CH and REM sleep less established.[97]
  - Patients with CH significantly suffer from obstructive sleep apnea.[98]
- Alcohol may precipitate CH attacks during active cluster periods.[99]
  - Some patients with chronic CH report high alcohol/tobacco consumption.[100]
- CH prodromes include AS and mild pain or nonpainful sensations in the area that subsequently becomes painful.[101]
  - Blurred vision, sensitivity to smells, nausea, dyspepsia, hunger, irritability, tiredness, and tenseness.[101]
  - Premonitory symptoms may predict CH days before onset, present in 40% of CH cases.
    - Similar to those experienced by migraineurs.[101]
      - "Auralike" symptoms in 14% of cases.[102]

Autonomic signs

- Ipsilateral lacrimation most frequent AS; in approximately 90% of cases.[94]
  - Common and pronounced in CH, subtler in other TACs.
  - Rarely ptosis and miosis (partial Horner syndrome) may persist.
  - Intensity of AS may be related to pain severity.[103]
- Migrainous features are common in CH.[104]
  - Photophobia, phonophobia, nausea, and vomiting in up to half of cases.
    - Phonophobia and photophobia are unilateral: in migraine bilateral.[105]
- CH associated with transient hemiparesis, visual symptoms, photophobia, phonophobia, and nausea.[104]
  - Strikingly similar to side-locked migraine.

Differential diagnosis and secondary CH

- Dental/Sinus pathology
  - May be related to referral patterns[87,89–92] and occurrence of "lower CH."[93]

Occur as a result of rare pathologies:

- Vascular lesions, multiple sclerosis,[86] pituitary tumor,[106] trauma.[107]
- Secondary TACs have no "typical" presentation; mimic primary TAC.[108,109]
  - Neuroimaging must be performed for all TACs or atypical[108,110,111] TAC-like syndromes.[112]

CH treatment

Nonpharmacologic treatment

- A clear explanation of mechanisms, treatment options, and prognosis (**Tables 3–5**).
- Based on attack patterns, patients avoid daytime naps.
- Avoid alcoholic beverages and other triggers.
- Altitude hypoxemia may trigger an attack during active periods, but may be pharmacologically prevented.[113]

Table 3
Selected abortive pharmacologic treatment options for episodic cluster headache

Agent	Dose	Comments	Side Effects
Oxygen (inhaled via face mask)	5–10 L/min 15 min 15 L/min may be tried	First line but cumbersome. Hyperbaric oxygen also efficacious but impractical.	None
Sumatriptan	6–12 mg SC	First line, fast, and efficacious; 12 mg as effective as 6 mg but with more side effects. Marginally less effective in chronic CH.	Contraindicated in CV disease. Fatigue Nausea/vomiting Chest symptoms Skin reactions over puncture wound.
	20 mg IN	Less effective but easier to use.	Contraindicated in CV disease. IN<SC
Zolmitriptan	5–10 mg IN	Limited efficacy, alternative to IN sumatriptan.	Contraindicated in CV disease. Better in episodic CH.
Dihydroergotamine	0.5–1.0 mg IN (bilateral)	Reduces severity but not frequency. Risk of rebound.	Contraindicated in CV disease. Do not use with a triptan.
Lignocaine	1 mL of 4%–10% solution applied IN on cotton pledget bilaterally	Pain is decreased but not enough studies. Needs to be inserted deep near pterygopalatine foramen.	Bitter taste

Abbreviations: CH, cluster headache; CV, cardiovascular; IN, intranasal; SC, subcutaneous injection.

Nonpharmacologic treatment[114,115]

- Abortive (first line)[114]
  - Rapid symptomatic relief with oxygen inhalation.[114]
    - Useful diagnostic test.
    - In resistant cases try higher flow rates (15 L/min).[116]
  - Subcutaneous sumatriptan if medically fit.
- Transitional and prophylactic[114]
  - Rapid transitional prophylaxis may be attained with corticosteroids.
    - For a limited period in selected patients.[117]
  - Long-term prophylaxis usually with verapamil[113] in both episodic and chronic CH.
    - Topiramate as second-line therapy.
    - Although many side effects, lithium carbonate may be considered.
- Surgical,[118] for carefully selected recalcitrant cases.

Recent reports indicate that medication overuse headache (MOH) is a possible complication in patients with CH and patients with other TACs.[119,120] Remission periods in many patients may increase with time, and beyond the age of 65 to 75, active CH is rare.

Table 4
Prophylactic treatment of episodic cluster headache

Agent	Target Dose	Comments	Side Effects
Verapamil	160–480 mg/d (PO)	First-line treatment. Perform baseline and 6 monthly ECGs.	Hypotension, bradycardia, heart block, dizziness, and fatigue
Prednisone	80 mg (PO) Typical schedule: 80 mg first 2 d. Reduce by 20 mg every 2 d. Reduce to 10 mg/d for last 2 d	Good for initial and transitional therapy until, eg, verapamil takes effect. Prolonged use not recommended because of side effects. Taper over 10–21 d.	Increased appetite, nervousness, hyperglycemia, insomnia, headaches
Topiramate	25–200 mg/d (PO)	Increase by 25 mg/d every 5 d.	Cognitive effects, paresthesias, dizziness
Valproic acid	600–2000 mg/d (PO)	Efficacious in patients with pronounced migrainous features. Monitor liver function.	Nausea, dizziness, dyspepsia, thrombocytopenia
Gabapentin	900 mg/d (PO)	Few studies but promising results.	Drowsiness
Melatonin	9–10 mg/d nocte (PO)	Few studies.	None

Abbreviations: ECG, electrocardiogram; nocte, nighttime; PO, orally.

PH

PH is rare, with an estimated prevalence of 2 to 20 per 100,000.[85,121–123] Mean age of onset is usually 34 to 41 years, but children aged 6 and adults aged 81 years have been reported with average illness duration of 13 years.[124–126] The episodic form is considered to have an earlier mean age of onset (27 years) than the chronic form (37 years).[124]

Only 20% of PHs behave episodically,[125] and many of these eventually develop into a chronic form.[124] The IHS requires at least 20 attacks that meet the criteria outlined.

Table 5
Treatment of chronic cluster headache

Agent	Target Dose	Comments	Side Effects
Verapamil	360–480 mg/d (PO)	First-line treatment. Perform baseline ECG.	Hypotension, bradycardia, heart block, dizziness, and fatigue
Lithium carbonate	300–900 mg (PO)	Requires monitoring of renal and thyroid function, and of serum concentrations (best at 0.4–0.8 mEq/L).	Weakness, nausea, tremor, slurred speech, blurred vision *Side effects > verapamil.*

Abbreviations: ECG, electrocardiogram; PO, orally.

Summary of PH features

- Unilateral, severe orbital, or periorbital pain.
  - Rarely may become bilateral.[127]
  - Also temporal, periauricular, maxillary, and, rarely, occipital areas.[125,128]
  - Referral to the shoulder, neck, and arm is quite common.[128]
  - Strong pain may cross the midline.
  - The vast majority of attacks do not change sides.[125]
- Last 2 to 30 minutes.
  - More usually 13 to 29 minutes, but may last nearly an hour.
  - Pain onset is rapid and mostly peaks in less than 5 minutes.[125]
- Sharp and excruciating.[125]
  - Also throbbing, stabbing, sharp, or boring.[125,129]
- Accompanied by at least 1 of the following ipsilateral autonomic signs:
  - Conjunctival injection/lacrimation
  - Nasal congestion/rhinorrhea
  - Eyelid edema
  - Forehead/facial sweating
  - Miosis and ptosis
- More than 5 attacks daily.
  - Usually 8 to 30 attacks per 24 hours.[124]
  - Seasonal pattern of attacks in PH patients has been described.[130]
  - The temporal similarity to CH behavior has led to the term "modified cluster pattern."[128]
  - 30% report REM-related[131] nocturnal attacks that wake.[124]
- Absolute response to indomethacin.

Additional features

AS may occur bilaterally but are more pronounced on the symptomatic side. The most commonly seen are ipsilateral lacrimation, nasal congestion, conjunctival injection, and rhinnorrhea.[129,132] In patient series, one "migrainous feature" was reported by nearly 90% of cases.[125,133]

Secondary paroxysmal hemicrania

- Malignancy, central nervous system disease, and benign tumors.[110]
- Parotid gland epidermoid carcinoma with cerebral metastasis.[134]
- Systemic diseases.[110,124]
- All PH cases require imaging.[135]

Treatment

The response of PH to indomethacin is absolute. Most cases respond within 24 hours, but 3 days at 75 mg followed, if needed, by 150 mg for a further 3 days is recommended as trial therapy[136]; high persistent dosage requirements may indicate underlying pathology. Prognosis in PH is good and long-term remission has been reported.[137] Indomethacin-resistant PH may respond to topiramate.[112,138,139] A summary of therapies for PH, SUNCT, and HC is shown in **Table 6**.

SUNCT

SUNCT syndrome is a unilateral headache/facial pain characterized by brief paroxysmal attacks accompanied by ipsilateral local AS, usually conjunctival injection and lacrimation.[140] The similarities of this syndrome to trigeminal neuralgia (TN) are

Table 6
Pharmacotherapy of PH, SUNCT, and HC

Headache	Drug of Choice	Target Dose (Route)	Second Line
PH	Indomethacin	75–225 mg/d (PO)	Other NSAIDs Verapamil Acetazolamide
SUNCT	Lamotrigine	100–300 mg/d (PO)	Gabapentin 900–2700 mg/d Topiramate 50–200 mg/d
HC	Indomethacin	25–300 mg/d (PO)	Other NSAIDs Piroxicam-beta-cyclodextrin

Abbreviations: HC, hemicrania continua; NSAID, nonsteroidal anti-inflammatory drug; PH, paroxysmal hemicranias; PO, orally; SUNCT, short-lasting neuralgiform headache attacks with conjunctival injection and tearing.

marked, particularly the triggering mechanism and many believe SUNCT to be a TN variant.[141]

Estimates suggest SUNCT/short-lasting, unilateral, neuralgiform headache attacks with cranial autonomic features (SUNA) to be as common as PH.[85] SUNCT is presently considered only slightly more common in men,[142,143] with a mean onset at approximately 50 years.[142,144] SUNCT occurring in siblings has recently been presented as "familial SUNCT."[145] The IHS requires at least 20 attacks that meet the criteria outlined.

Clinical features of SUNCT

- Unilateral, ocular/periocular pain,[1] but may involve most head areas.[146]
  - Pain spreading across the midline or changing sides is rare.[142]
- Moderate to severe pain[142]; less severe than TN.
- Pain accompanied by ipsilateral conjunctival injection and lacrimation.
- Usually stabbing or pulsating.
  - Sometimes electric or burning.[142]
- Lasts from 5 to 240 seconds.
  - Usually 15 to 120 seconds (mean 1 minute).
  - Longer attacks of up to 10 minutes and even 2 to 3 hours reported.[147]
  - "SUNCT status"; (rare) pain most of the day for 1 to 3 days.[148]
  - Low-grade background pain/discomfort occurs.[148]
- Three patterns of attacks described.[112,146]
  - Classical single attacks.
  - Groups of a number of stabs/attacks.
  - "Saw-tooth" pattern with numerous stabs/attacks lasting minutes.
- Frequency is from 3 to 200 daily.
  - Inconsistent and irregular; average of 28 per day.[147]
  - A bimodal distribution of attacks occurring in the morning and late afternoon has been observed.
  - Fewer than 2% of attacks occur at night.[147]
  - A "clusterlike" pattern has been reported with active and inactive periods.[140]
  - A seasonal pattern has been reported in SUNA.[149]

Additional features

Pain in SUNCT may be triggered by light mechanical stimuli in the areas innervated by the trigeminal nerve but with a short latency until pain onset.[142] Extratrigeminal

triggers, including neck movements, have also been shown to precipitate attacks. No refractory period has been demonstrated in SUNCT.[142,150]

By definition, SUNCT is accompanied by marked ipsilateral conjunctival injection and lacrimation that appear rapidly with onset of pain.[1] Nasal stuffiness and rhinorrhea are common; sweating may accompany attacks but is rare and often subclinical.[140,151]

SUNA

This is a relatively novel diagnostic entity included in the IHS classification's appendix. Essentially 2 criteria differentiate it from SUNCT: SUNA may be accompanied by any autonomic sign (eg, nasal congestion), and attack duration has been extended to up until 10 minutes.[1,112,120,146]

Secondary SUNCT/SUNA

- Brainstem infarction.
- Cerebellopontine region: arteriovenous malformations, astrocytoma, or other tumors/cysts.
- Cavernous hemangioma of the brainstem.
- Cavernous sinus tumor, extraorbital cystic mass, vertebral artery dissection, and neurofibromatosis.[110,142,152,153]
- Posttraumatic.[142]
- All patients with SUNCT should be referred for imaging.[142]

SUNCT/SUNA treatment

- Lamotrigine is the drug of choice (see **Table 6**).[112,154]
  - Initial dosage is 25 mg per day; increase very slowly, reach target in 7 or more weeks.
- SUNCT may respond to steroids.[155]
- Anticonvulsant drugs may produce some improvement.
  - Carbamazepine, topiramate, and gabapentin (see **Table 6**).[112]
- Case reports of successful surgical microvascular decompression and percutaneous trigeminal ganglion compression for SUNCT.[156]
- Remissions have been observed and may last for several months.[157,158]

HC

As HC is further reported, this headache entity is increasingly considered a TAC variant.[1] As in other TACs, HC seems to be often misdiagnosed and mistreated; in a recent series, time to correct diagnosis was 5 years.[159]

Clinical features of HC

- Unilateral headache for more than 3 months.
  - Pain in the frontal and temporal regions and periorbitally.[160]
  - Although *very rare*, pain can also change sides.[161] Few bilateral cases.
- Daily and continuous pain.
- Severity is moderate (VAS 4.7).[162]
  - Characterized (74%) by fluctuations in pain severity.
  - Exacerbations are totally disabling in about 40% of patients.[162]
  - Exacerbations result in severe pain (VAS 9.3) lasting 30 minutes to 10 hours and even up to 2 to 5 days.[86,162]
  - During exacerbation, HC is almost indistinguishable from migraine.[162]
  - Patients may report a sharp pain similar to the condition of "jabs and jolts."[162]

- Some patients (18%) describe a distinct ocular sensation mimicking a foreign body (or sand), that may accompany or precede the headaches.[86]
- Pain is throbbing (one-third of cases); may appear as pain intensity increases.[86,162]
- Complete response to indomethacin.
- During exacerbations, accompanied by at least 1 of the following ipsilateral autonomic phenomena/signs:
  - Conjunctival injection/lacrimation
  - Nasal congestion/rhinorrhea
  - Miosis and ptosis

Additional features

Two forms of HC have been described: remitting and continuous. The remitting form is characterized by headache that can last for some days followed by a pain-free period lasting from 2 to 15 days.[86,162] One-third of remitting cases become continuous following a mean duration of 7.8 years.[86,162] Nocturnal attacks were reported in up to half of patients.[86,162]

HC is not usually accompanied by notable pathology or other abnormalities.[86] Most published cases of HC with computerized scanning of the head, neurologic and other physical examination, hematology, and serum biochemistry were all normal. Cases of HC secondary to pathology or systemic disease have been reported.[110]

There is usually a paucity of AS in HC. However, during exacerbation, AS commonly appear singly or in various combinations, but are still relatively mild. This strengthens the hypothesis that activation of AS is dependent on pain severity. The most common signs present in 30% to 40% of patients are photophobia, nausea, conjunctival injection, phonophobia, and tearing.[86] During exacerbations up to 60% of patients display qualities such as photophobia, phonophobia, nausea, and, more rarely, vomiting.[162] HC with aura has also been described, further linking HC to migraine pathophysiology.[163] More rarely (15%–18%) nasal stuffiness or rhinorrhea, vomiting, or ptosis may also be reported.[86] These features establish the HC phenotype as straddling both TACs and migraine.

Secondary hemicrania continua

- Medication abuse.[86]
- Mesenchymal tumor in the sphenoid bone has been reported.[86]
- Head trauma and surgery.[86,162]

Treatment

- Indomethacin totally effective.[1]
  - Relief occurs within hours or 1 to 2 days.
- Other NSAIDs are less effective.[164]
- Piroxicam-beta-cyclodextrin is a good alternative for selected cases.[165]

Differential diagnosis of TACs

Given the predominate sensory system involved, referral patterns of TACs often involve orofacial structures and at times may primarily present in intraoral or unusual facial sites. Thus, CH and PH have caused misdiagnosis as dental pain leading to unnecessary dental interventions.[87,90,92,94] Cluster headaches are often seen by ear, nose, and throat surgeons and erroneously diagnosed as sinus pathology.[87,90,92,94]

TTHS

The IHS subclassifies TTH into episodic (infrequent and frequent), chronic, and probable TTH. The individual attacks in these subentities have similar clinical features with some subtle differences; severity and the occurrence of mild nausea tend to increase with frequency. Pericranial muscle tenderness is an extremely common feature in patients with TTH, but because some patients do not demonstrate this feature, the IHS subclassifies TTH as with or without pericranial tenderness.

TTH is extremely common, and most individuals will have experienced one in their lifetime.[166] TTH has a 1-year prevalence in adults of more than 80%, higher than migraine.[166,167] Infrequent episodic TTH (IETTH), which occurs on average once per month, is most common (48%–59%) but does not usually require medical attention.[168,169] One-year prevalence of frequent episodic TTH (FETTH) is 18% to 43% and 10% to 25% report weekly headaches.[169,170] TTH, in particular chronic TTH (CTTH), is thought to account for more than 10% of disease-related absenteeism.[171]

The average onset age of TTH is 20 to 30 years with peak prevalence in the third to fifth decades.[168] However, up to 25% of school children report having TTH,[172] and in the older population (>60 years) the prevalence is 20% to 30%.

Genetic studies reveal that first-degree relatives of CTTH sufferers are 3 times as likely to also suffer headaches relative to the population.[173] FETTH is significantly affected by environmental factors, with evidence for only a minor genetic contribution.[174]

Episodic Tension-Type Headache

Clinical features

- Bilateral in >90%.
- Occipital, parietal, temporal or frontal areas.[19,175]
  - "Bandlike" or "caplike."
  - Site may vary with intensity.[175]
- Pressurelike, dull or tight.[175]
  - Throbbing is rare and related to severity.[175,176]
- Intensity is mild to moderate.[19,177]
  - Increases with headache frequency.[178]
- Duration 30 minutes to 7 days.[179]
- 25% of episodic TTH (ETTH) evolves into CTTH.[170,180]
- Sleep disturbances.[181]
- Mild to moderate anorexia.[19]
- Occasional and mild photophobia (10%) or phonophobia (7%).[19,175]

Many patients will suffer both migraines and TTH, which may further affect quality of life. Interestingly, ETTH in migraine sufferers responds to sumatriptan, a migraine-specific drug, whereas in patients who do not suffer from migraine, it does not.[182] This may suggest that mild migraines may phenotypically be very similar to ETTH.

ETTH is commonly precipitated by a number of factors: stress, fatigue, disturbed meals, menstruation, alcohol, and a lack of sleep.[31,40] Although TTH is usually not aggravated by physical activity,[175] there are reports that in some patients with TTH, exercise may aggravate pain.[183,184]

Other than in location, TTH is very similar to masticatory myofascial pain.

CTTH

CTTH is one of the subtypes of a group simply termed "chronic daily headaches," based on the daily or near daily occurrence of headaches.

Clinical features of CTTH

Classically, the patient with CTTH is middle-aged and female, with a long headache history that began with episodic headaches 10 to 20 years previously and slowly increased in frequency.[54,58,185] The clinical features of CTTH are largely similar to those in FETTH, with differences in accompanying features, treatment response, and impact on quality of life.

- CTTH is bilateral.
  - Frontal, temporal, or frontotemporal regions.[19,58,186]
- Pressurelike.[19]
- Mostly moderate pain.
  - <10% severe.[19,187]
- Continuous or daily headache.
  - Mean frequency is 23 to 30 headache days per month.[186,188]
- Increased pericranial tenderness.[189]
- Photophobia or phonophobia.[190]
- Physical activity may worsen pain in some patients with CTTH.[19,187]
- Depression, anxiety, and lack of sleep common.[191]

Pathophysiology

Interrelationships between peripheral and central mechanisms probably underlie the initiation of TTHs, but the exact etiology is uncertain.[192,193] The evidence suggests that peripheral mechanisms play a major role in ETTHs, whereas central mechanisms, such as faulty inhibitory mechanisms and central sensitization, are prominent in CTTH.[194] It is interesting to note that the same etiologic factors are considered in TTH and in masticatory myofascial pain (MMP), further suggesting common pathophysiology.

Treatment of TTH

- Pharmacologic
  - Abortive therapy
    - 800 mg ibuprofen or 825 mg naproxen.[195]
    - 1 g of paracetamol.[196]
    - Triptans for CTTH, or mixed migraine and ETTH.[197,198]
  - Prophylactic
    - Tricyclic antidepressants are efficacious.[199]
      - Effective in CTTH but not in ETTH.
      - 10 mg daily taken just before bedtime and then titrated.
        - CTTH may need up to 75 mg.[200]
    - Muscle relaxants and botulinum toxin,[201] mixed results.

Nonpharmacological interventions

- Behavioral.[202]
  - Relaxation training.
    - Relaxation and electromyographic biofeedback therapies are effective mainly in ETTH.[203]
  - Biofeedback training.
  - Cognitive-behavioral (stress-management) therapy.
    - In patients with CTTH, the combination of stress management with a tricyclic antidepressant (amitriptyline $\leq$100 mg/d, or nortriptyline $\leq$75 mg/d) induced significant reductions in headache index scores than each therapy alone or placebo.[204]

- Physiotherapy, massage therapy, acupuncture, or chiropractic manipulation may be beneficial for TTH, but the evidence is weak.[205]

- Temporomandibular disorder therapies.
  - Occlusal splints or physiotherapy.[206]
    - Reduction in severity and frequency of headaches.
  - No significant effect of occlusal adjustment was observed on headache frequency.[207]

REFERENCES

1. The International classification of headache disorders. 2nd edition. 2004. Available at: http://ihs-classification.org/en/. Accessed October 9, 2011.
2. Henry P, Michel P, Brochet B, et al. A nationwide survey of migraine in France: prevalence and clinical features in adults. GRIM. Cephalalgia 1992;12(4): 229–37 [discussion: 186].
3. O'Brien B, Goeree R, Streiner D. Prevalence of migraine headache in Canada: a population-based survey. Int J Epidemiol 1994;23(5):1020–6.
4. Stewart WF, Lipton RB, Celentano DD, et al. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA 1992;267(1):64–9.
5. Rasmussen BK, Jensen R, Schroll M, et al. Epidemiology of headache in a general population—a prevalence study. J Clin Epidemiol 1991;44(11):1147–57.
6. Olesen J. The migraines: introduction. In: Olesen J, Tfelt-Hansen P, Welch KM, editors. The headaches. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 223–5.
7. Cavallini A, Micieli G, Bussone G, et al. Headache and quality of life. Headache 1995;35(1):29–35.
8. Steiner TJ. Headache burdens and bearers. Funct Neurol 2000;15(Suppl 3): 219–23.
9. Steiner TJ, Scher AI, Stewart WF, et al. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia 2003;23(7):519–27.
10. Russell MB, Olesen J. Increased familial risk and evidence of genetic factor in migraine. BMJ 1995;311(7004):541–4.
11. Stewart WF, Staffa J, Lipton RB, et al. Familial risk of migraine: a population-based study. Ann Neurol 1997;41(2):166–72.
12. Estevez M, Gardner KL. Update on the genetics of migraine. Hum Genet 2004; 114(3):225–35.
13. Mochi M, Cevoli S, Cortelli P, et al. A genetic association study of migraine with dopamine receptor 4, dopamine transporter and dopamine-beta-hydroxylase genes. Neurol Sci 2003;23(6):301–5.
14. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: an electronic diary study. Neurology 2003;60(6):935–40.
15. Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. Headache 2004;44(9):865–72.
16. Kelman L. The aura: a tertiary care study of 952 migraine patients. Cephalalgia 2004;24(9):728–34.
17. Kelman L. Migraine pain location: a tertiary care study of 1283 migraineurs. Headache 2005;45(8):1038–47.
18. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 1992;12(4):221–8 [discussion: 186].

19. Rasmussen BK, Jensen R, Olesen J. A population-based analysis of the diagnostic criteria of the International Headache Society. Cephalalgia 1991;11(3): 129–34.
20. Russell MB, Rasmussen BK, Fenger K, et al. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. Cephalalgia 1996; 16(4):239–45.
21. Stewart WF, Lipton RB, Kolodner K. Migraine disability assessment (MIDAS) score: relation to headache frequency, pain intensity, and headache symptoms. Headache 2003;43(3):258–65.
22. Rasmussen BK, Olesen J. Symptomatic and nonsymptomatic headaches in a general population. Neurology 1992;42(6):1225–31.
23. Zagami AS, Rasmussen BK. Symptomatology of migraine. In: Olesen J, Tfelt-Hansen P, Welch KM, editors. The headaches. 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 337–43.
24. Pryse-Phillips W, Findlay H, Tugwell P, et al. A Canadian population survey on the clinical, epidemiologic and societal impact of migraine and tension-type headache. Can J Neurol Sci 1992;19(3):333–9.
25. Rasmussen P. Facial pain. IV. A prospective study of 1052 patients with a view of: precipitating factors, associated symptoms, objective psychiatric and neurological symptoms. Acta Neurochir (Wien) 1991;108(3–4):100–9.
26. Barbanti P, Fabbrini G, Pesare M, et al. Unilateral cranial autonomic symptoms in migraine. Cephalalgia 2002;22(4):256–9.
27. Kaup AO, Mathew NT, Levyman C, et al. 'Side locked' migraine and trigeminal autonomic cephalgias: evidence for clinical overlap. Cephalalgia 2003;23(1): 43–9.
28. Martin VT, Behbehani MM. Toward a rational understanding of migraine trigger factors. Med Clin North Am 2001;85(4):911–41.
29. Chabriat H, Danchot J, Michel P, et al. Precipitating factors of headache. A prospective study in a national control-matched survey in migraineurs and nonmigraineurs. Headache 1999;39(5):335–8.
30. Rasmussen BK. Migraine and tension-type headache in a general population: precipitating factors, female hormones, sleep pattern and relation to lifestyle. Pain 1993;53(1):65–72.
31. Spierings EL, Ranke AH, Honkoop PC. Precipitating and aggravating factors of migraine versus tension-type headache. Headache 2001;41(6):554–8.
32. Kelman L, Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. Headache 2005;45(7): 904–10.
33. Dodick DW, Eross EJ, Parish JM, et al. Clinical, anatomical, and physiologic relationship between sleep and headache. Headache 2003;43(3):282–92.
34. Granella F, Sances G, Allais G, et al. Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres. Cephalalgia 2004;24(9):707–16.
35. Couturier EG, Bomhof MA, Neven AK, et al. Menstrual migraine in a representative Dutch population sample: prevalence, disability and treatment. Cephalalgia 2003;23(4):302–8.
36. Martin VT, Wernke S, Mandell K, et al. Defining the relationship between ovarian hormones and migraine headache. Headache 2005;45(9):1190–201.
37. Granella F, Sances G, Pucci E, et al. Migraine with aura and reproductive life events: a case control study. Cephalalgia 2000;20(8):701–7.

38. Robbins L. Precipitating factors in migraine: a retrospective review of 494 patients. Headache 1994;34(4):214–6.
39. Rasmussen BK. Epidemiology of headache. Cephalalgia 2001;21(7):774–7.
40. Karli N, Zarifoglu M, Calisir N, et al. Comparison of pre-headache phases and trigger factors of migraine and episodic tension-type headache: do they share similar clinical pathophysiology? Cephalalgia 2005;25(6):444–51.
41. Zebenholzer K, Wober C, Kienbacher C, et al. Migrainous disorder and headache of the tension-type not fulfilling the criteria: a follow-up study in children and adolescents. Cephalalgia 2000;20(7):611–6.
42. Benoliel R, Elishoov H, Sharav Y. Orofacial pain with vascular-type features. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;84(5):506–12.
43. Penarrocha M, Bandres A, Penarrocha M, et al. Lower-half facial migraine: a report of 11 cases. J Oral Maxillofac Surg 2004;62(12):1453–6.
44. Daudia AT, Jones NS. Facial migraine in a rhinological setting. Clin Otolaryngol Allied Sci 2002;27(6):521–5.
45. Lance JW, Goadsby PJ. Mechanism and management of headache. 7th edition. Philadelphia: Elsevier; 2005.
46. Eross E, Dodick D, Eross M. The Sinus, Allergy and Migraine Study (SAMS). Headache 2007;47(2):213–24.
47. Schreiber CP, Hutchinson S, Webster CJ, et al. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "sinus" headache. Arch Intern Med 2004;164(16):1769–72.
48. Campbell JK, Sakai F. The migraines: diagnosis and differential diagnosis. In: Olesen J, Tfelt-Hansen P, Welch KM, editors. The headaches. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2000.
49. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache. American Academy of Neurology; 2000. Available at: http://www.aan.com/professionals/practice/pdfs/gl0088.pdf. Accessed May 17, 2013.
50. Sandrini G, Friberg L, Janig W, et al. Neurophysiological tests and neuroimaging procedures in non-acute headache: guidelines and recommendations. Eur J Neurol 2004;11(4):217–24.
51. Lipton RB, Pan J. Is migraine a progressive brain disease? JAMA 2004;291(4):493–4.
52. Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. Headache 2005;45(Suppl 1):S3–13.
53. Katsarava Z, Schneeweiss S, Kurth T, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology 2004;62(5):788–90.
54. Scher AI, Stewart WF, Ricci JA, et al. Factors associated with the onset and remission of chronic daily headache in a population-based study. Pain 2003;106(1–2):81–9.
55. Krymchantowski AV, Moreira PF. Clinical presentation of transformed migraine: possible differences among male and female patients. Cephalalgia 2001;21(5):558–66.
56. Spierings EL, Schroevers M, Honkoop PC, et al. Presentation of chronic daily headache: a clinical study. Headache 1998;38(3):191–6.
57. Mathew NT, Reuveni U, Perez F. Transformed or evolutive migraine. Headache 1987;27(2):102–6.
58. Solomon S, Lipton RB, Newman LC. Clinical features of chronic daily headache. Headache 1992;32(7):325–9.

59. Srikiatkhachorn A, Phanthumchinda K. Prevalence and clinical features of chronic daily headache in a headache clinic. Headache 1997;37(5):277–80.
60. Peres MF, Sanchez del Rio M, Seabra ML, et al. Hypothalamic involvement in chronic migraine. J Neurol Neurosurg Psychiatry 2001;71(6):747–51.
61. Merikangas KR, Rasmussen BK. Migraine comorbidity. In: Olesen J, Tfelt-Hansen P, Welch KM, editors. The headaches. 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 235–40.
62. Scher AI, Bigal ME, Lipton RB. Comorbidity of migraine. Curr Opin Neurol 2005; 18(3):305–10.
63. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol 2012;75:365–91.
64. Edvinsson L, Villalon CM, Maassenvandenbrink A. Basic mechanisms of migraine and its acute treatment. Pharmacol Ther 2012;136(3):319–33.
65. Pryse-Phillips WE, Dodick DW, Edmeads JG, et al. Guidelines for the nonpharmacologic management of migraine in clinical practice. Canadian Headache Society. CMAJ 1998;159(1):47–54.
66. Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78(17): 1346–53.
67. Dodick DW, Lipton RB, Ferrari MD, et al. Prioritizing treatment attributes and their impact on selecting an oral triptan: results from the TRIPSTAR Project. Curr Pain Headache Rep 2004;8(6):435–42.
68. Ferrari MD, Goadsby PJ, Roon KI, et al. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia 2002;22(8):633–58.
69. Savi L, Omboni S, Lisotto C, et al. Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, crossover, multicenter, Italian, comparative study versus rizatriptan. J Headache Pain 2011;12(6):609–15.
70. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78(17):1337–45.
71. MacGregor EA, Pawsey SP, Campbell JC, et al. Safety and tolerability of frovatriptan in the acute treatment of migraine and prevention of menstrual migraine: results of a new analysis of data from five previously published studies. Gend Med 2010;7(2):88–108.
72. US Headache Consortium. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. American Academy of Neurology; 2000. Available at: http://www.aan.com/professionals/practice/pdfs/gl0090.pdf. Accessed October 2005.
73. Silberstein SD, Goadsby PJ, Lipton RB. Management of migraine: an algorithmic approach. Neurology 2000;55(9 Suppl 2):S46–52.
74. Loder E, Biondi D. General principles of migraine management: the changing role of prevention. Headache 2005;45(Suppl 1):S33–47.
75. Welch KM, Nagesh V, Aurora SK, et al. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 2001;41(7):629–37.
76. Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis. Cochrane Database Syst Rev 2004;(3):CD003226.

77. Silberstein SD, Goadsby PJ. Migraine: preventive treatment. Cephalalgia 2002; 22(7):491–512.
78. Goadsby PJ. Advances in the understanding of headache. Br Med Bull 2005; 73–74:83–92.
79. Dahlof CG. Management of primary headaches: current and future aspects. In: Giamberardino MA, editor. Pain 2002- An updated review: refresher course. Seattle (WA): IASP Press; 2002. p. 85–112.
80. Leone M, Proietti Cecchini A, Franzini A, et al. From neuroimaging to patients' bench: what we have learnt from trigemino-autonomic pain syndromes. Neurol Sci 2012;33(Suppl 1):S99–102.
81. Holle D, Katsarava Z, Obermann M. The hypothalamus: specific or nonspecific role in the pathophysiology of trigeminal autonomic cephalalgias? Curr Pain Headache Rep 2011;15(2):101–7.
82. Leone M, Bussone G. Pathophysiology of trigeminal autonomic cephalalgias. Lancet Neurol 2009;8(8):755–64.
83. Manzoni GC, Terzano MG, Bono G, et al. Cluster headache—clinical findings in 180 patients. Cephalalgia 1983;3(1):21–30.
84. Fischera M, Marziniak M, Gralow I, et al. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. Cephalalgia 2008; 28(6):614–8.
85. Sjaastad O, Bakketeig LS. Cluster headache prevalence. Vaga study of headache epidemiology. Cephalalgia 2003;23(7):528–33.
86. Benoliel R, Sharav Y. Trigeminal autonomic cephalgias (TACs). In: Sharav Y, Benoliel R, editors. Orofacial pain and headache. Edinburgh (United Kingdom): Mosby Elsevier; 2008. p. 223–54.
87. van Vliet JA, Eekers PJ, Haan J, et al. Features involved in the diagnostic delay of cluster headache. J Neurol Neurosurg Psychiatry 2003;74(8):1123–5.
88. Manzoni GC, Micieli G, Granella F, et al. Cluster headache—course over ten years in 189 patients. Cephalalgia 1991;11(4):169–74.
89. Bahra A, Goadsby PJ. Diagnostic delays and mis-management in cluster headache. Acta Neurol Scand 2004;109(3):175–9.
90. Klapper JA, Klapper A, Voss T. The misdiagnosis of cluster headache: a nonclinic, population-based, Internet survey. Headache 2000;40(9):730–5.
91. Larner AJ. Trigeminal autonomic cephalalgias: frequency in a general neurology clinic setting. J Headache Pain 2008;9(5):325–6.
92. Van Alboom E, Louis P, Van Zandijcke M, et al. Diagnostic and therapeutic trajectory of cluster headache patients in Flanders. Acta Neurol Belg 2009; 109(1):10–7.
93. Cademartiri C, Torelli P, Cologno D, et al. Upper and lower cluster headache: clinical and pathogenetic observations in 608 patients. Headache 2002;42(7):630–7.
94. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. Neurology 2002;58(3):354–61.
95. Torelli P, Manzoni GC. Pain and behaviour in cluster headache. A prospective study and review of the literature. Funct Neurol 2003;18(4):205–10.
96. Russell D. Cluster headache: severity and temporal profiles of attacks and patient activity prior to and during attacks. Cephalalgia 1981;1(4):209–16.
97. Pfaffenrath V, Pollmann W, Ruther E, et al. Onset of nocturnal attacks of chronic cluster headache in relation to sleep stages. Acta Neurol Scand 1986;73(4):403–7.
98. Chervin RD, Zallek SN, Lin X, et al. Timing patterns of cluster headaches and association with symptoms of obstructive sleep apnea. Sleep Res Online 2000;3(3):107–12.

99. Schurks M, Diener HC. Cluster headache and lifestyle habits. Curr Pain Headache Rep 2008;12(2):115–21.
100. Torelli P, Cologno D, Cademartiri C, et al. Possible predictive factors in the evolution of episodic to chronic cluster headache. Headache 2000;40(10): 798–808.
101. Blau JN, Engel HO. Premonitory and prodromal symptoms in cluster headache. Cephalalgia 1998;18(2):91–3 [discussion: 71–2].
102. Langedijk M, van der Naalt J, Luijckx GJ, et al. Cluster-like headache aura status. Headache 2005;45(1):80–1.
103. Drummond PD. Dissociation between pain and autonomic disturbances in cluster headache. Headache 1990;30(8):505–8.
104. Wheeler SD. Significance of migrainous features in cluster headache: divalproex responsiveness. Headache 1998;38(7):547–51.
105. Irimia P, Cittadini E, Paemeleire K, et al. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. Cephalalgia 2008;28(6):626–30.
106. Levy MJ, Matharu MS, Meeran K, et al. The clinical characteristics of headache in patients with pituitary tumours. Brain 2005;128(Pt 8):1921–30.
107. Manzoni GC. Cluster headache and lifestyle: remarks on a population of 374 male patients. Cephalalgia 1999;19(2):88–94.
108. Cittadini E, Matharu MS. Symptomatic trigeminal autonomic cephalalgias. Neurologist 2009;15(6):305–12.
109. Favier I, van Vliet JA, Roon KI, et al. Trigeminal autonomic cephalgias due to structural lesions: a review of 31 cases. Arch Neurol 2007;64(1):25–31.
110. Trucco M, Mainardi F, Maggioni F, et al. Chronic paroxysmal hemicrania, hemicrania continua and SUNCT syndrome in association with other pathologies: a review. Cephalalgia 2004;24(3):173–84.
111. Wilbrink LA, Ferrari MD, Kruit MC, et al. Neuroimaging in trigeminal autonomic cephalgias: when, how, and of what? Curr Opin Neurol 2009;22(3):247–53.
112. Goadsby PJ, Cittadini E, Cohen AS. Trigeminal autonomic cephalalgias: paroxysmal hemicrania, SUNCT/SUNA, and hemicrania continua. Semin Neurol 2010; 30(2):186–91.
113. Dodick DW, Rozen TD, Goadsby PJ, et al. Cluster headache. Cephalalgia 2000; 20(9):787–803.
114. Ashkenazi A, Schwedt T. Cluster headache—acute and prophylactic therapy. Headache 2011;51(2):272–86.
115. Rozen TD. Trigeminal autonomic cephalalgias. Neurol Clin 2009;27(2):537–56.
116. Rozen TD. High oxygen flow rates for cluster headache. Neurology 2004;63(3): 593.
117. Antonaci F, Costa A, Candeloro E, et al. Single high-dose steroid treatment in episodic cluster headache. Cephalalgia 2005;25(4):290–5.
118. Benoliel R. Trigeminal autonomic cephalgias. B J Pain 2012;6(3):106–23.
119. Paemeleire K, Evers S, Goadsby PJ. Medication-overuse headache in patients with cluster headache. Curr Pain Headache Rep 2008;12(2):122–7.
120. Goadsby PJ, Cittadini E, Burns B, et al. Trigeminal autonomic cephalalgias: diagnostic and therapeutic developments. Curr Opin Neurol 2008;21(3): 323–30.
121. Koopman JS, Dieleman JP, Huygen FJ, et al. Incidence of facial pain in the general population. Pain 2009;147(1–3):122–7.
122. Obermann M, Katsarava Z. Epidemiology of unilateral headaches. Expert Rev Neurother 2008;8(9):1313–20.

123. Sjaastad O, Bakketeig LS. The rare, unilateral headaches. Vaga study of headache epidemiology. J Headache Pain 2007;8(1):19–27.
124. Antonaci F, Sjaastad O. Chronic paroxysmal hemicrania (CPH): a review of the clinical manifestations. Headache 1989;29(10):648–56.
125. Boes CJ, Dodick DW. Refining the clinical spectrum of chronic paroxysmal hemicrania: a review of 74 patients. Headache 2002;42(8):699–708.
126. Kudrow DB, Kudrow L. Successful aspirin prophylaxis in a child with chronic paroxysmal hemicrania. Headache 1989;29(5):280–1.
127. Matharu MS, Goadsby PJ. Bilateral paroxysmal hemicrania or bilateral paroxysmal cephalgia, another novel indomethacin-responsive primary headache syndrome? Cephalalgia 2005;25(2):79–81.
128. Boes CJ, Vincent M, Russell D. Chronic paroxysmal hemicrania. In: Olesen J, Goadsby PJ, Ramadan NM, et al, editors. The headaches. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 815–22.
129. Sarlani E, Schwartz AH, Greenspan JD, et al. Chronic paroxysmal hemicrania: a case report and review of the literature. J Orofac Pain 2003;17(1):74–8.
130. Siow HC. Seasonal episodic paroxysmal hemicrania responding to cyclooxygenase-2 inhibitors. Cephalalgia 2004;24(5):414–5.
131. Sahota PK, Dexter JD. Sleep and headache syndromes: a clinical review. Headache 1990;30(2):80–4.
132. Benoliel R, Sharav Y. Paroxysmal hemicrania. Case studies and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85(3):285–92.
133. Cittadini E, Matharu MS, Goadsby PJ. Paroxysmal hemicrania: a prospective clinical study of 31 cases. Brain 2008;131(Pt 4):1142–55.
134. Mariano da Silva H, Benevides-Luz I, Santos AC, et al. Chronic paroxysmal hemicrania as a manifestation of intracranial parotid gland carcinoma metastasis—a case report. Cephalalgia 2004;24(3):223–7.
135. Gatzonis S, Mitsikostas DD, Ilias A, et al. Two more secondary headaches mimicking chronic paroxysmal hemicrania. Is this the exception or the rule? Headache 1996;36(8):511–3.
136. Pareja J, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua. Interval between indomethacin administration and response. Headache 1996; 36(1):20–3.
137. Sjaastad O, Antonaci F. Chronic paroxysmal hemicrania: a case report. Long-lasting remission in the chronic stage. Cephalalgia 1987;7(3):203–5.
138. Camarda C, Camarda R, Monastero R. Chronic paroxysmal hemicrania and hemicrania continua responding to topiramate: two case reports. Clin Neurol Neurosurg 2008;110(1):88–91.
139. Cohen AS, Goadsby PJ. Paroxysmal hemicrania responding to topiramate. J Neurol Neurosurg Psychiatry 2007;78(1):96–7.
140. Sjaastad O, Saunte C, Salvesen R, et al. Shortlasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, sweating, and rhinorrhea. Cephalalgia 1989;9(2):147–56.
141. Sjaastad O, Kruszewski P. Trigeminal neuralgia and “SUNCT” syndrome: similarities and differences in the clinical pictures. An overview. Funct Neurol 1992; 7(2):103–7.
142. Pareja JA, Cuadrado ML. SUNCT syndrome: an update. Expert Opin Pharmacother 2005;6(4):591–9.
143. Matharu MS, Cohen AS, Boes CJ, et al. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome: a review. Curr Pain Headache Rep 2003;7(4):308–18.

144. D'Andrea G, Granella F. SUNCT syndrome: the first case in childhood. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. Cephalalgia 2001;21(6):701–2.
145. Gantenbein AR, Goadsby PJ. Familial SUNCT. Cephalalgia 2005;25(6):457–9.
146. Cohen AS, Matharu MS, Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA)–a prospective clinical study of SUNCT and SUNA. Brain 2006;129(Pt 10):2746–60.
147. Pareja JA, Shen JM, Kruszewski P, et al. SUNCT syndrome: duration, frequency, and temporal distribution of attacks. Headache 1996;36(3):161–5.
148. Pareja JA, Caballero V, Sjaastad O. SUNCT syndrome. Statuslike pattern. Headache 1996;36(10):622–4.
149. Baldacci F, Nuti A, Lucetti C, et al. SUNA syndrome with seasonal pattern. Headache 2009;49(6):912–4.
150. Benoliel R, Sharav Y. Trigeminal neuralgia with lacrimation or SUNCT syndrome? Cephalalgia 1998;18(2):85–90.
151. Kruszewski P, Zhao JM, Shen JM, et al. SUNCT syndrome: forehead sweating pattern. Cephalalgia 1993;13(2):108–13.
152. Jacob S, Rajabally Y. Short-lasting unilateral neuralgiform headache with cranial autonomic symptoms (SUNA) following vertebral artery dissection. Cephalalgia 2007;27(3):283–5.
153. Jimenez Caballero PE, Portilla Cuenca JC, Casado Naranjo I. Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) secondary to epidermoid cyst in the right cerebellopontine angle successfully treated with surgery. J Headache Pain 2011;12(3):385–7.
154. Williams MH, Broadley SA. SUNCT and SUNA: clinical features and medical treatment. J Clin Neurosci 2008;15(5):526–34.
155. Pareja JA, Kruszewski P, Sjaastad O. SUNCT syndrome: trials of drugs and anesthetic blockades. Headache 1995;35(3):138–42.
156. Morales-Asin F, Espada F, Lopez-Obarrio LA, et al. A SUNCT case with response to surgical treatment. Cephalalgia 2000;20(1):67–8.
157. Benoliel R, Sharav Y. SUNCT syndrome: case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85(2):158–61.
158. Pareja JA, Sjaastad O. SUNCT syndrome. A clinical review. Headache 1997; 37(4):195–202.
159. Rossi P, Faroni J, Tassorelli C, et al. Diagnostic delay and suboptimal management in a referral population with hemicrania continua. Headache 2009;49(2):227–34.
160. Newman LC, Lipton RB, Solomon S. Hemicrania continua: ten new cases and a review of the literature. Neurology 1994;44(11):2111–4.
161. Newman LC, Lipton RB, Russell M, et al. Hemicrania continua: attacks may alternate sides [see comments]. Headache 1992;32(5):237–8.
162. Peres MF, Silberstein SD, Nahmias S, et al. Hemicrania continua is not that rare. Neurology 2001;57(6):948–51.
163. Peres MF, Siow HC, Rozen TD. Hemicrania continua with aura. Cephalalgia 2002;22(3):246–8.
164. Peres MF, Silberstein SD. Hemicrania continua responds to cyclooxygenase-2 inhibitors. Headache 2002;42(6):530–1.
165. Sjaastad O, Antonaci F. A piroxicam derivative partly effective in chronic paroxysmal hemicrania and hemicrania continua. Headache 1995;35(9):549–50.
166. Rasmussen BK. Epidemiology of headache. Cephalalgia 1995;15(1):45–68.

167. Lyngberg AC, Rasmussen BK, Jorgensen T, et al. Incidence of primary headache: a Danish epidemiologic follow-up study. Am J Epidemiol 2005;161(11): 1066–73.
168. Lyngberg AC, Rasmussen BK, Jorgensen T, et al. Has the prevalence of migraine and tension-type headache changed over a 12-year period? A Danish population survey. Eur J Epidemiol 2005;20(3):243–9.
169. Russell MB. Tension-type headache in 40-year-olds: a Danish population-based sample of 4000. J Headache Pain 2005;6(6):441–7.
170. Jensen R, Symon D. Epidemiology of tension-type headache. In: Olesen J, Goadsby PJ, Ramadan NM, et al, editors. The headaches. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 621–4.
171. Rasmussen BK, Jensen R, Olesen J. Impact of headache on sickness absence and utilisation of medical services: a Danish population study. J Epidemiol Community Health 1992;46(4):443–6.
172. Stovner LJ, Zwart JA, Hagen K, et al. Epidemiology of headache in Europe. Eur J Neurol 2006;13(4):333–45.
173. Ostergaard S, Russell MB, Bendtsen L, et al. Comparison of first degree relatives and spouses of people with chronic tension headache. BMJ 1997; 314(7087):1092–3.
174. Ulrich V, Gervil M, Olesen J. The relative influence of environment and genes in episodic tension-type headache. Neurology 2004;62(11):2065–9.
175. Iversen HK, Langemark M, Andersson PG, et al. Clinical characteristics of migraine and episodic tension-type headache in relation to old and new diagnostic criteria. Headache 1990;30(8):514–9.
176. Inan LE, Tulunay FC, Guvener A, et al. Characteristics of headache in migraine without aura and episodic tension-type headache in the Turkish population according to the IHS classification. Cephalalgia 1994;14(2):171–3.
177. Gobel H, Petersen-Braun M, Soyka D. The epidemiology of headache in Germany: a nationwide survey of a representative sample on the basis of the headache classification of the International Headache Society. Cephalalgia 1994; 14(2):97–106.
178. Rasmussen BK. Migraine and tension-type headache are separate disorders. Cephalalgia 1996;16(4):217–20 [discussion: 223].
179. Olesen J, Bousser MG, Diener HC, et al. The International classification of headache disorders, 2nd edition. Cephalalgia 2004;24(Suppl 1):24–150.
180. Couch JR. The long-term prognosis of tension-type headache. Curr Pain Headache Rep 2005;9(6):436–41.
181. Lipton RB, Cady RK, Stewart WF, et al. Diagnostic lessons from the spectrum study. Neurology 2002;58(9 Suppl 6):S27–31.
182. Lipton RB, Stewart WF, Cady R, et al. 2000 Wolfe Award. Sumatriptan for the range of headaches in migraine sufferers: results of the Spectrum Study. Headache 2000;40(10):783–91.
183. Ulrich V, Russell MB, Jensen R, et al. A comparison of tension-type headache in migraineurs and in non-migraineurs: a population-based study. Pain 1996; 67(2–3):501–6.
184. Koseoglu E, Nacar M, Talaslioglu A, et al. Epidemiological and clinical characteristics of migraine and tension type headache in 1146 females in Kayseri, Turkey. Cephalalgia 2003;23(5):381–8.
185. Bigal ME, Sheftell FD, Rapoport AM, et al. Chronic daily headache in a tertiary care population: correlation between the International Headache Society

diagnostic criteria and proposed revisions of criteria for chronic daily headache. Cephalalgia 2002;22(6):432–8.
186. Bendtsen L, Jensen R. Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache. Neurology 2004;62(10):1706–11.
187. Manzoni GC, Granella F, Sandrini G, et al. Classification of chronic daily headache by International Headache Society criteria: limits and new proposals. Cephalalgia 1995;15(1):37–43.
188. Jensen R, Rasmussen BK. Muscular disorders in tension-type headache. Cephalalgia 1996;16(2):97–103.
189. Bendtsen L, Jensen R, Olesen J. Decreased pain detection and tolerance thresholds in chronic tension-type headache. Arch Neurol 1996;53(4):373–6.
190. Langemark M, Olesen J, Poulsen DL, et al. Clinical characterization of patients with chronic tension headache. Headache 1988;28(9):590–6.
191. de Filippis S, Salvatori E, Coloprisco G, et al. Headache and mood disorders. J Headache Pain 2005;6(4):250–3.
192. Bendtsen L, Fernandez-de-la-Penas C. The role of muscles in tension-type headache. Curr Pain Headache Rep 2011;15(6):451–8.
193. Bezov D, Ashina S, Jensen R, et al. Pain perception studies in tension-type headache. Headache 2011;51(2):262–71.
194. Kaniecki RG. Tension-type headache. Continuum 2012;18(4):823–34.
195. Mathew NT, Ashina M. Acute pharmacotherapy of tension-type headaches. In: Olesen J, Goadsby PJ, Ramadan NM, et al, editors. The headaches. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 727–33.
196. Steiner TJ, Lange R, Voelker M. Aspirin in episodic tension-type headache: placebo-controlled dose-ranging comparison with paracetamol. Cephalalgia 2003;23(1):59–66.
197. Brennum J, Kjeldsen M, Olesen J. The 5-HT1-like agonist sumatriptan has a significant effect in chronic tension-type headache. Cephalalgia 1992;12(6):375–9.
198. Cady RK, Gutterman D, Saiers JA, et al. Responsiveness of non-IHS migraine and tension-type headache to sumatriptan. Cephalalgia 1997;17(5):588–90.
199. Tomkins GE, Jackson JL, O'Malley PG, et al. Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med 2001;111(1):54–63.
200. Fumal A, Schoenen J. Chronic tension-type headache. In: Goadsby PJ, Silberstein SD, Dodick D, editors. Chronic daily headache. Hamilton (Canada): BC Decker Inc; 2005. p. 57–64.
201. Stillman MJ. Pharmacotherapy of tension-type headaches. Curr Pain Headache Rep 2002;6(5):408–13.
202. Holroyd KA. Behavioral and psychologic aspects of the pathophysiology and management of tension-type headache. Curr Pain Headache Rep 2002;6(5):401–7.
203. Bogaards MC, ter Kuile MM. Treatment of recurrent tension headache: a meta-analytic review. Clin J Pain 1994;10(3):174–90.
204. Holroyd KA, O'Donnell FJ, Stensland M, et al. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. JAMA 2001;285(17):2208–15.
205. Fernandez-de-Las-Penas C, Alonso-Blanco C, Cuadrado ML, et al. Are manual therapies effective in reducing pain from tension-type headache?: a systematic review. Clin J Pain 2006;22(3):278–85.

206. Magnusson T, Carlsson GE. A 2 1/2-year follow-up of changes in headache and mandibular dysfunction after stomatognathic treatment. J Prosthet Dent 1983; 49(3):398–402.
207. Vallon D, Ekberg E, Nilner M, et al. Occlusal adjustment in patients with craniomandibular disorders including headaches. A 3- and 6-month follow-up. Acta Odontol Scand 1995;53(1):55–9.