The Treatment of Trigeminal Autonomic Cephalalgias: An Overview

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Trigeminal autonomic cephalalgias (TACs) are primary headaches that include cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks (SUNHAs) with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA). Hemicrania continua (HC) is another form that has been ascribed to TACs for clinical and pathophysiologic reasons. Cluster headache is the most common of these syndromes, even if comparatively rare, with a lifetime prevalence of around 1 in 1,000. TACs share many aspects from a pathophysiologic standpoint (a hypothalamic activation may be involved in all forms initiating the attacks), but differences in attack duration and frequency and in extent of treatment response distinguish one from the other. This review focuses on the treatments currently available for these headaches according to the most recent guidelines. Due to the low frequency of most TACs, there are little data from randomized controlled trials; therefore, evidence from simple open studies in small case series or single-case observations are reported. Promising results have been recently obtained with novel modes of drug administration, invasive pericranial interventions, and different strategies such as neurostimulation. There are also some future treatments being studied at present.
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Trigeminal autonomic cephalalgias (TACs) are primary headaches characterized by unilateral pain occurring in association with ipsilateral cranial autonomic features such as conjunctival injection, lacrimation, and/or nasal symptoms.[1,2] According to the third International Classification of Headache Disorders (ICHD-3),[3] TACs include cluster headache (CH), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks (SUNHAs) with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA), and hemicrania continua (HC). HC was previously classified under other primary headache disorders; only recently was it included in the TAC group due to clinical and pathophysiologic presentations very close to other forms.

CH is the most common of these syndromes, with a mean prevalence of 0.1% in the general population,[4] a clear preference for male gender,[5] and a male-to-female ratio of 2.5 to 7.1:1.[6,7] The lifetime incidence is 124 per 100,000, and the 1-year incidence is 53 per 100,000.[8] The onset of CH is usually in young adulthood, with a peak incidence at around 30 years in males. The prevalence rates of PH and SUNCT are much lower than CH, but these could be underrated due to the frequent misdiagnosis of trigeminal neuralgia as CH. There is limited information about the prevalence of CH and SUNCT/SUNA, but these forms of headache are certainly rare, with a total of only a few hundred cases having been reported.

Several observations, including family and twin studies, suggest a genetic component in CH, but the mode of transmission is variable.[9] First-degree relatives of CH patients have between 14- and 39-fold increased risk of CH.[10,11] Presently, the genetic basis for PH, SUNCT, and HC is unknown, although some case series of familial TACs have been reported.

TACs are distinguished from one another by the frequency and duration of the attacks, as well as the response to treatments. However, all these forms are characterized by severe pain and disability, and thus also poor quality of life.[12] For this reason, the goal of treatment is to interrupt pain in the acute phase using symptomatic drugs and to prevent it using prophylactic drugs.

Clinical Features and Diagnosis

CH is characterized by severe or unbearable and tightly unilateral pain, typically in the retro-orbital and frontotemporal areas and associated with ipsilateral symptoms and signs of cranial autonomic dysfunction (ie, conjunctival injection, tearing, eyelid edema, miosis, ptosis, nasal congestion, rhinorrhea, and facial sweating). In addition, during the attacks there is a typical sense of restlessness and agitation. The attacks last 15 to 180 minutes, show a characteristic circadian periodicity, and may occur up to eight times a day. In CH the attacks tend to cluster together into bouts with different durations. If the bouts last 7 to 365 days and are separated by pain-free remission periods of more than 1 month, the form is defined as episodic CH (ECH); if they recur over more than 1 year without remission periods or with remission periods lasting less than 1 month, the form is defined as chronic CH (CCH).[3] Most CH attacks are spontaneous, but some of them may be triggered by alcohol intake, volatile substances such as solvents or oil-based paints, and/or nitroglycerin acting as nitric oxide (NO) donor.[13,14]

The diagnosis of CH is mostly clinical and based on the IHS diagnostic criteria,[3] which are reported in Table 1. There is now agreement that the occurrence of only a single cluster period is sufficient to diagnose CH. In the absence of specific treatments, periods should last from 7 to 365 days with a pain-free remission period of at least 1 month.[3] Thus, there is often a considerable diagnostic delay in CH,[15] and it can be initially unrecognized or misdiagnosed as migraine.

PH is characterized by relatively short (2 to 30 minutes) attacks of very severe unilateral pain in retro-orbital or frontotemporal regions. Occasionally, the pain may radiate to the neck or ipsilateral shoulder and usually has an abrupt onset and cessation. Most attacks are spontaneous, but some of them may be triggered by rotating the neck, by flexing the head, or by an external pressure applied in the cervical region. Residual mild pain may remain between attacks. Attack frequency ranges from 1 to 40 per day, and the most common autonomic symptoms associated with these attacks are tearing and nasal congestion. Symptoms typically respond to indomethacin[16] (Table 2). Like CH, PH also occurs in two forms: episodic (EPH) and chronic (CPH). Most patients (80%) have CPH, with no remission of attacks within 1 year or remissions lasting less than 1 month.

HC, recently included in TACs, is characterized by a continuous, strictly unilateral head pain lasting at least 3 months, with exacerbation periods occurring that range from many times per week to a few times per month. Pain affects the temporal or periorbital area and is mild or moderate in intensity with no headache-related disability. Excellent response to indomethacin is a characteristic feature of this form and is included in the IHS diagnostic criteria[3] (Table 3). During the exacerbation periods, an increase in pain lasting hours or days and the appearance of associated migrainous or autonomic symptoms may occur. Photophobia and phonophobia are the predominant migrainous symptoms, followed by nausea and vomiting. The most common autonomic symptoms are tearing and nasal congestion.[17] Interparoxysmal pain that mostly occurs in PH may simulate the continuous pain of HC, but the background pain of HC is usually more severe than the interparoxysmal pain of PH; moreover, pain exacerbations of HC are longer than those of PH. When strictly applying the ICHD criteria, the two forms can be easily distinguished.

Finally, SUNHAs include two entities, SUNCT and SUNA. SUNCT is a TAC with very short-lasting, lateralized, and severe pain-recurrent attacks lasting up to 600 seconds. Attack frequency ranges from 3 to 200 per day, and the headache stab may last up to 10 minutes.[18] The pain involves the periocular region and is often triggered by cutaneous stimuli.[18] By definition, the autonomic symptoms most frequently associated are tearing and conjunctival injection, but sometimes other parasympathetic signs may occur due to an overexpression of the trigeminal-autonomic reflex (ie, nasal congestion, rhinorrhea, eyelid edema, and facial redness). If only one or neither tearing nor conjunctival injection is present, a diagnosis of SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms) can be formulated (Table 4). Like CH and PH, SUNCT and SUNA show two modes of presentation—episodic or chronic—according to the above-mentioned temporal criteria.

The differential diagnosis of CH—unlike other primary headaches, migraine without aura, and trigeminal neuralgia—is complicated by the existence of secondary headaches; eg, those caused by an inflammatory process of the cavernous sinus or the paranasal sinuses, which can simulate the signs and symptoms of CH and sometimes of other TACs (Fig 1). In addition, CH may initially display atypical attack frequency and duration; it is therefore mandatory

Table 1 Diagnostic Criteria for Cluster Headache According to the International Headache Society[3]

A	At least five headache attacks fulfilling criteria B–D
B	Severe or very severe unilateral orbital, supraorbital, and/or temporal headache pain lasting 15 to 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	Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
E	Not better accounted for by another ICHD-3 diagnosis

Table 2 Diagnostic Criteria for Paroxysmal Hemicrania According to the International Headache Society[3]

A	At least 20 attacks fulfilling criteria B–E
B	Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2 to 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
E	Not better accounted for by another ICHD-3 diagnosis
F	Prevented absolutely by therapeutic doses of indomethacin

Table 3 Diagnostic Criteria for Hemicrania Continua According to the International Headache Society[3]

A	Unilateral headache fulfilling criteria B–D
B	Presenting 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

Table 4 Diagnostic Criteria for Short-Lasting Unilateral Neuralgiform Headache Attacks According to the International Headache Society[3]

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 to 600 seconds and occurring as single stabs, series of stabs, or in a saw-tooth pattern
C	At least on of the following symptoms or signs ipsilateral to the headache: a) Conjunctival injection and/or lacrimation b) Nasal conjestion and/or rhinorrhea c) Eylid edema d) Forehead and facial sweating e) Miosis and or ptosis
D	Occurring with a frequency of at least one a day
E	Not better accounted for by another ICHD-3 diagnosis

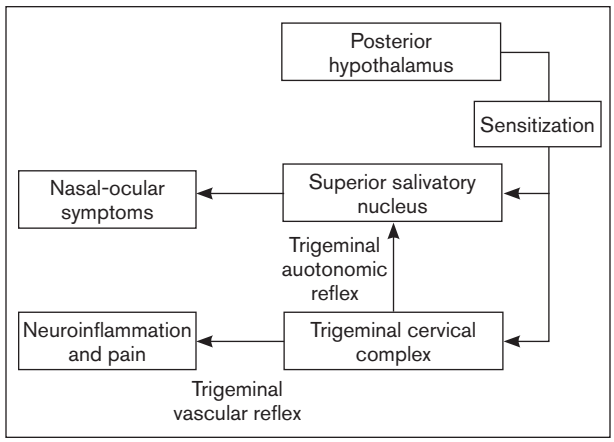

Fig 1 The direct activation of the posterior hypothalamus, as supported by consistent findings of functional imaging studies, results in a lowering of the activation threshold of the superior salivatory nucleus and the trigeminal cervical complex (ie, sensitization). In turn, this permissive state allows the antidromic release of CGRP and substance P from the projections of sensory trigeminal fibers in the vessel walls (trigeminal vascular reflex), causing neurogenic inflammation (neuroinflammation) and pain. Moreover, the activation of the superior salivatory nucleus directly or indirectly through the trigeminal autonomic reflex results in an increased firing of parasympathetic fibers and thus in the autonomic ipsilateral signs (conjunctival injection, tearing, nasal congestion, and rhinorrhea) typical of TACs.

to obtain magnetic resonance imaging (MRI) of the brain and of the intracranial vessels. Migraine without aura, especially its chronic form, may at times be misdiagnosed as a TAC, but migraine attacks show a longer duration of symptoms (4 to 72 hours), and local autonomic signs and the typical periodicity are

absent. Visual or other auras have been reported to occur in association with CH (also in the form of Alice in Wonderland syndrome) as well as with HC and CPH,[19] and sometimes this may make it difficult to reach a diagnosis, particularly with regard to migraine with aura. On the other hand, trigeminal neuralgia is characterized by severe burning or electric shock–like pain attacks, localized in one or more divisions of the trigeminal nerve. To make a correct differential diagnosis among TACs, the temporal criterion is extremely important, even if there may be an overlap in the duration of the attacks among the different forms. Another useful diagnostic tool is the response to indomethacin (≥ 150 mg per os or ≥ 100 mg intramuscularly): this drug is able to completely prevent the pain episodes in PH and HC. Administration of indomethacin (INDOtest) can thus be used as an ex juvantibus rule to strengthen diagnostic power.[20]

In summary, the differential diagnosis between CH and other forms of primary and secondary headaches can be relatively simple in the presence of clear clinical features and a normal MRI, but can be particularly difficult in the initial forms with atypical clinical presentations.

TACs and the Orofacial Area

Atypical or ectopic pain localization of TACs has been repeatedly reported in the literature. Of interest, the orofacial area has been described as being involved in several TACs, whereby signs and symptoms fulfill (except for pain localization) the ICHD-3 criteria of definite CH. This is the case, for instance, of episodic toothache seen by dentists,[21,22] which is partly reminiscent of the lower syndrome variant of CH previously described by another author.[23,24] The real nature of TACs for these clinical presentations has been questioned, but pain characteristics, time patterns, accompanying autonomic symptoms, and response to therapy (oxygen, steroids, dihydroergotamine) appear to be consistent with the definition of orofacial CH.[21,22] The pathophysiology of these forms is unclear, but the occurrence of a somatotopic rearrangement of afferent nociceptive endings in the brainstem has been claimed, where perioral areas are represented in the rostral part of the trigeminal nucleus caudalis and afferents of lateral face regions relay more caudally. Thus, in CH, pain may not be restricted to the first trigeminal division, but extend from the orbital to the maxillary or mandibular areas subserved by the orofacial trigeminal divisions, similar to what was observed for the convergence of trigeminal and upper cervical pain roots in the cervical spinal root that may explain CH pain localization in occipital areas.[25] Since these attacks do not completely fulfill the current pain localization criteria, a diagnosis of only probable CH (ICHD-3 code 3.5) can be put forward. Although the current classification recognizes in the comments the possibility that pain may spread to other regions,[3] a clear statement of a possible orofacial localization of pain in the diagnostic criteria would be reasonable.

A predominant/exclusive orofacial location of pain has also been reported for CPH, where pain—typically responsive to indomethacin administration—can be located in the maxillary area and misdiagnosed as reflecting dental pathology or temporomandibular joint disorders.[26,27] As recently pointed out,[28] orofacial manifestations of primary headache disorders and primary facial pain disorders are distinct entities. There are definitely common trigeminal inputs, but then a differentiation occurs, possibly due to a somatotopic segregation at the level of the trigeminal nucleus, thalamus, and somatosensory cortex. Different neurochemical pathways may also be involved in this process. Structural and functional imaging studies, as well as the development of new therapies for TACs, will probably help in answering these questions.

In the meantime, it should be borne in mind that, after neurologists, dentists and ear-nose-throat specialists are the physicians most frequently consulted by patients with TACs at the onset of disease.[15,29] This may in part account for the delay reported in making a correct diagnosis, since these professionals may be less familiar with TACs. Medical misdiagnosis (ie, doctor delay)[15] remains one of the main problems for TACs, often resulting in mismanagement of the disease.[7]

Treatment of CH

The therapeutic management of CH is usually divided into acute, transitional, and prophylactic treatments.

Acute Attacks

The drugs of this group are aimed to be rapidly effective in interrupting the headache attack. For this purpose, oral medications are not suitable, as the therapeutic agent should be promptly bioavailable. Therefore, drugs parenterally administered are preferred. The main objectives of a correct symptomatic treatment are to obtain pain relief as soon as possible and to avoid or limit to a minimum the adverse events[7] (Table 5).

Sumatriptan. Sumatriptan acts on serotonin 5-hydroxytriptamine (5-HT) receptors 5-HT1B[30] with a vasoconstrictive effect on small- and medium-sized arteries, such as those supplying the cerebral cortex. In addition, as a 5-HT1D receptor agonist, it inhibits

the neuronal release of vasoactive peptides such as calcitonin gene-related peptide (CGRP), substance P, and neurokinin A.[31] These mechanisms are relevant to the effect of sumatriptan on pain in CH patients. Sumatriptan subcutaneous injection has a time of maximal concentration of 12 minutes with a half-life of approximately 2 hours. The drug is metabolized in the liver and gastrointestinal tract by monoamine oxidase type A (MAO-A) and excreted by both the liver and kidney. Its high efficacy in the management of acute attack made it a drug of first choice in the symptomatic treatment of CH. A randomized, placebo-controlled trial (RCT) compared sumatriptan 6 mg to placebo and found a decrease of headache severity within 15 minutes in 74% of sumatriptan-treated patients vs 26% of placebo-treated patients. Besides, a significantly higher proportion of sumatriptan-treated patients were pain free 15 minutes after injection compared to placebo-treated patients (46% vs 10%).[32] In another RCT, sumatriptan was evaluated at greater doses (12 mg), and, although a relief was also observed in this case (80% vs 35%), no significant difference of efficacy was demonstrated between patients treated with 12 mg and those treated with 6 mg of sumatriptan. On the contrary, the higher dose of sumatriptan was associated with more numerous adverse effects.[33] The continued use of sumatriptan subcutaneous injections for acute treatment of CH did not show any reduction of drug efficacy over time and did not present any increase of adverse effects for high-use frequencies.[34] In summary, subcutaneous sumatriptan is effective in the treatment of acute attacks of CH; the recommended dose for the treatment of a single attack is 6 mg; and higher doses are not associated with a better efficacy, only more adverse effects.

Intranasal sumatriptan was also found effective in the acute treatment of CH. In an RCT,[35] patients with episodic and chronic CH were treated with intranasal sumatriptan 20 mg in a nostril; in over 154 attacks analyzed, headache response was significantly higher for sumatriptan than for placebo (57% vs 26%). Moreover, pain-free remission at the same time was 47% and 18%, respectively. However, the slower onset of action and the lower efficacy suggest its use for attacks lasting at least 45 minutes.

An alternative method of delivery for sumatriptan is available in several countries. It is a pre-filled, single-use, disposable, needle-free subcutaneous system delivering sterile sumatriptan injection. It eliminates the needle and disposal issues, appears to improve drug delivery, and shows acceptable tolerability for patients in clinical trials.[36] The advantage of this method is to allow for a rapid C_{max}, thus obtaining an earlier therapeutic response.

Sumatriptan is contraindicated in patients with coronary artery disease or cerebrovascular disease because of its vasoconstrictive effect on coronary and cerebral arteries. A clinical evaluation of the risk of vascular diseases is to be done in all patients before prescribing the drug. In fact, triptan-associated serious cardiovascular adverse events are mostly seen in patients with pre-existing major cardiovascular risk factors or with established cardiac or cerebrovascular disease. There is a small risk of serotonin syndrome when SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs) are co-prescribed with triptans, but current evidence does not deter from using these drugs concomitantly.[37]

Table 5 Levels of Evidence for Symptomatic and Preventive Treatments of Cluster Headache[7,50]

Drug	Dosage	Level of evidence
Symptomatic treatments		
Sumatriptan	6 mg s.c.	A
Sumatriptan	20 mg nasal spray	A
Zolmitriptan	5–10 mg nasal spray	A
Oxygen inhalation	7–10 l/min for 15 min	A
Octreotide	100 µg s.c.	B
Lidocaine	1 mL (4% to 10%) nasal spray	B
Preventive treatments		
Verapamil	200–900 mg per os	A
Lithium carbonate	600–900 mg per os	B
Valproic acid	500–2,000 mg per os	C
Topiramate	50–200 mg per os	B
Baclofen	15–30 mg per os	C
Melatonin	10 mg per os	C

Level A = requires at least one convincing Class I study or at least two consistent, convincing Class II studies.
Level B = requires at least one convincing Class II study or overwhelming Class III evidence.
Level C = requires at least two convincing Class III studies.

Zolmitriptan. Oral zolmitriptan was tested as an acute treatment for CH attacks and was found to be effective in the episodic form, but not in CCH patients.[38] Thirty minutes after administration, headache response rates in ECH patients were 47% and 29% for zolmitriptan 10 mg and placebo, respectively. No effect of oral zolmitriptan was observed in CCH patients. The most common adverse effects reported for zolmitriptan, as well as for other triptans, were paresthesias, asthenia, nausea, dizziness, and chest tightness.

Zolmitriptan nasal spray is an effective therapeutic opportunity for the acute treatment of CH. Patients treated with intranasal zolmitriptan at a dose of 5 or 10 mg had headache relief after 30 minutes that was significantly higher than placebo-treated patients (62% and 40% vs 21%, respectively).[39] Similar results were found in a second RCT in 52 patients with CH.[40] Zolmitriptan is well tolerated by this route

of administration; sometimes bad taste (22%) and nasal cavity discomfort (12%) are reported.

Like sumatriptan, zolmitriptan is contraindicated in patients with notable risk of vascular disease. In these cases, other acute treatments should be preferred.

Oxygen. Oxygen inhalation is recognized as one of the first-choice treatments for acute attacks of CH. Its efficacy in aborting the attacks was described for the first time in the '50s[41] and confirmed in the '80s in controlled studies that compared 100% oxygen at 7 liters/minute for 15 minutes to room air.[42] In placebo-controlled trials,[43,44] oxygen at high flows (from 12 up to 14–15 liters/minute) given via a non-rebreather face mask produced a statistically significant response to headache, with full or substantial pain relief in 78% of patients. Hyperbaric oxygen (HBO) has also been studied as a treatment for acute attacks of CH; it showed to be useful not only for interrupting the attacks, but also for ending the cluster period (in 3 of 6 patients) in a placebo-controlled study.[45] In clinical practice, a gender difference was reported in response to oxygen; ie, only 59% in female CH patients and up to 87% in male CH patients.[46] Recently, however, it has been stated that while normobaric oxygen inhalation is effective in CH attacks, the use of HBO is not supported by sufficient data.[47] The mechanism of action through which inhaled oxygen is able to interrupt the acute attack of CH is still unknown. However, oxygen is likely to work like an arterial vasoconstrictive agent, and hyperoxia might inhibit plasma protein extravasation elicited by the activation of the trigeminal-vascular reflex.[48,49]

In summary, inhaled oxygen represents an effective treatment of an acute attack of CH, producing fast pain relief either at standard flow or, in the absence of a response, at high flow, with no substantial adverse effects. Therefore, oxygen is a useful alternative in patients with elevated vascular risk in whom the treatment with triptans is contraindicated. Attention is to be paid to patients with chronic obstructive pulmonary disease because of the risk of respiratory depression.

Ergotamine and Dihydroergotamine. A controlled study compared the efficacy of sublingual ergotamine to that of oxygen in patients with CH. No significant difference in efficacy was found between the two treatments, with a positive response in 70% of ergotamine-treated patients.[50] Various formulations of dihydroergotamine were used in the treatment of the acute attack of CH: intravenous, intramuscular, subcutaneous, or intranasal. Clinical experience suggests that dihydroergotamine may be effective in acute CH treatment, mainly by intravenous route. Evidence derived from controlled studies indicates that intranasal dihydroergotamine 1 mg is moderately effective in reducing intensity, but not duration, of attacks.[51]

Similar to triptans, ergot derivatives exert their action by interacting with serotoninergic receptors, mainly 5-HT1B and 5-HT1D.[52,53] The agonistic effect on 5-HT1B receptors results in the constriction of extracerebral blood vessels in the meninges provided with algogenic nervous fibers, whereas the 5-HT1D receptors mediate the presynaptic inhibition on the trigeminal cervical complex, reducing the trigeminal-vascular reflex and the autonomic outflow from the nucleus tractus solitarius[54] (Fig 1).

Because the ergots, particularly ergotamine, also interact with α-adrenergic and 5-HT2A receptors preferentially expressed in extracranial vessels (eg, coronary arteries), adverse effects related to their vasoconstrictive action are more important than those of triptans. Therefore, ergots should never be used in patients with coronary, cerebral, and/or peripheral vascular disease; pregnancy; renal or hepatic failure; uncontrolled hypertension; or in rare forms of migraine, such as basilar or hemiplegic migraine.[52]

Anesthetics. Lidocaine locally applied to the sphenopalatine fossa[53] or self-administered by patients in the nostril ipsilateral to the pain[56] were found to be effective in patients with NTG-induced CH attacks. Better results were obtained with 10% lidocaine applied bilaterally to the sphenopalatine fossa using anterior rhinoscopy.[57] Similarly, the application of a solution of cocaine 10% in both nostrils was shown to interrupt the attack.[58] Cocaine is provided with sympathomimetic activity via modulation of reuptake of noradrenaline in nerve endings, whereas lidocaine appears to exert its effect via conduction-blocking properties. Although no significant adverse events were recorded, the risk of addiction for cocaine administration, especially in a disabling condition such as CH, should be obviously kept in mind, and the administration should be restricted to selected cases.

Somatostatin and Analogs. Somatostatin and one of its analogs, octreotide, were evaluated for the treatment of acute CH attacks. Intravenous somatostatin (25 μg in 50-mL saline) and subcutaneous octreotide (100 μg) were shown to be effective in inducing a significant reduction of pain 20 to 30 minutes after administration.[59,60] The mechanism of action of these peptides is unknown, but somatostatin appears to inhibit the release of numerous vasoactive peptides, including CGRP.[61] Due to the absence of vasoconstrictive effects, both somatostatin and octreotide may be used as alternatives to subcutaneous sumatriptan in the acute treatment of CH in patients with high vascular risk. However, attention is to be paid for the possible occurrences of hyperglycemia, abdominal pain, and/or diarrhea.

In conclusion, first-line drugs for the acute treatment of CH attacks are subcutaneous sumatriptan 6 mg, intranasal sumatriptan 20 mg, intranasal

zolmitriptan 5 or 10 mg, and 100% oxygen (level of evidence A; Table 2). Patients refractory to these first-line treatments can benefit from either subcutaneous octreotide or intranasal lidocaine 10% as alternative therapy.[7,62] The choice of treatment is obviously led by a patient's individual characteristics; eg, the presence of clinical comorbidities or of other ongoing therapies. In particular, the presence of vascular risk factors should be considered, since they can contraindicate the use of both triptans and ergot derivatives. For all these drugs, when the attack frequency tends to increase, it is also important to monitor the monthly intake for the risk of medication overuse, at least in patients with coexisting CH and migraine.

Preventive Treatment. Although symptomatic drugs, like triptans or oxygen, were shown to be effective in the treatment of acute attack of CH, they were not shown to modify the natural history of the disease or to affect the duration of the cluster periods. In the episodic form, a symptomatic treatment alone may be enough for active phases of short duration (mini-cluster), but long clusters of CCH require a preventive treatment. The latter is aimed at inducing a rapid break of active periods and a significant reduction in frequency, intensity, and duration of attacks.[7,63] Both experimental evidence and clinical experience have suggested some general rules in the management of CH prophylaxis[7,64]: preventive treatment should start early in the active phase and continue for at least 2 weeks after disappearance of attacks; later, treatment should be reduced gradually and then suspended, then re-initiated at the reappearance of attacks. The choice of the treatment should be made according to the expected duration of the cluster period, the response to previous treatments, any reported adverse effects, and any known comorbidities. The preventive treatment of CH is based on a transitional and long-term prophylaxis.

Transitional Prophylaxis. Because time is needed before the effect of preventive treatment takes place and often because it must be titrated slowly to avoid adverse effects, the patient may remain deprived of prophylactic drugs for days or weeks. For this purpose, the transitional prophylaxis works as bridge therapy with the aim to quickly interrupt pain attacks and to maintain pain relief until the prophylactic drug has become effective.

Corticosteroids. In patients with ECH or CCH, oral prednisone at doses ranging from 10 mg/day to 80 mg/day produced a significant reduction (72%) or a complete remission (58%) of attacks within 3 to 10 days. A burden prednisone dosage of at least 40 mg for 3 to 10 days, then tapered over 10 to 30 days, is sufficient to control the attacks.[65] Intravenous methylprednisolone at high doses (30 mg/kg over 3 hours) was found to interrupt the attacks in most treated patients, with a complete cluster remission in some of them.[66] Lower intravenous doses of methylprednisolone (250 mg in 100-mL saline) followed by prednisone per os (10 mg/day) were shown as an effective additional therapy in patients already treated with optimal doses of verapamil.[67]

The efficacy of steroids in CH is probably based on the anti-inflammatory action and the inhibition of the immune system, by which steroids hamper the release of vasoactive peptides produced by the trigeminal-vascular reflex.[68–73] In addition, steroids were also found to reduce the release of nitric oxide (NO), a gas involved in the regulation of vascular tone and modulation of nociception.[74]

Dihydroergotamine and Ergotamine Tartrate. Dihydroergotamine was studied as transitional therapy in an open-label study in ECH and CCH patients. Repetitive intravenous administration (0.5 mg three times per day) resulted in absence of pain in 35% of patients during the first day, in 69% by the second day, and in all patients within 5 days. After almost 3 months, over 90% of ECH patients and 44% of CCH patients remained headache-free.[75] Intranasal (1 mg) and subcutaneous (0.5 to 1 mg) routes of administration were also found to be effective, inducing the disappearance of attacks or a reduction of > 50% of attacks in 88% of patients with ECH and 57% of patients with CCH.[76] Reported adverse effects were mild; eg, nausea, chest tightness, and metallic taste. Ergotamine tartrate at a total daily dose of 3 to 4 mg for 2 to 3 weeks was shown to be a moderately effective transitional therapy.[77]

Long-term Prophylaxis

The aim of preventive treatments is to modify the natural evolution of CH by interfering with the mechanisms underlying the disease. The pharmacologic action is focused on the cluster periods in order to reduce frequency and severity of the attacks and to provide many CH patients with a significantly improved quality of life. As reported above, long-term prophylaxis is widely associated with a transitional therapy to attain this goal, but it may not be enough. Sometimes it is necessary to combine different drugs in a polytherapy in order to obtain good control of the attacks and clusters.

Verapamil. Verapamil is a calcium antagonist that interferes with slow calcium channels (voltage-operated). It was shown to be an effective long-term treatment in the prevention of CH (level of evidence A).[7] In a placebo-controlled study, a daily dose of 360 mg of verapamil significantly reduced the headache frequency in ECH patients treated for 2 weeks, and substantial or complete relief from pain was observed in half of the patients during the first week of treatment.[78] In patients with CCH, verapamil was found to

be better than lithium carbonate in controlling the attacks, with faster action and fewer side effects (50% vs 37%, respectively).[79] In these studies, however, dosages were higher than those used for the episodic form (up to 960 to 1,200 mg). The common use of verapamil as a therapy for maintenance of CH comes from its wide therapeutic window, which makes it safe and manageable. The rare adverse effects reported in the literature are due to its cardiovascular effects, mainly antiarrhythmic and vasodilatatory (ie, hypotension, peripheral edema, and bradycardia). For this reason, it is important that patients are carefully evaluated with regard to blood pressure, heart rate, and the possible presence of branch blocks before starting the drug. To this purpose, an ECG should be obtained both at baseline and during the titration of therapy.

Some observations indicate that the mechanism of action of verapamil is largely independent of its effect on the vascular bed. Indeed, it exerts its action mainly modulating the activity of central neurons via interactions with muscarinic, serotoninergic, and dopaminergic receptors and inhibits presynaptic adrenergic receptors, thereby increasing noradrenaline release.[80,81] This effect is further enhanced by the interaction with the opioid system, which modulates the pain pathways via changes in endorphin levels and restoration of the pain control system.[82]

Lithium Carbonate. The use of lithium carbonate in the treatment of CH goes back to the '70s, when the drug was used for the first time in this disease following previous observations of its effectiveness in other disorders with a classical cyclic pattern (ie, bipolar disorder and disorders of sleep-wake rhythm).[83,84] Lithium is indeed the first-line treatment of bipolar disorder according to considerable evidence.[85] Moreover, although not as notably as in the case of migraine,[86] CH is characterized by psychiatric comorbidity, particularly with regard to periodic affective illness.[84] After an initial success in patients with CCH in whom the treatment led to a significant improvement in headache frequency and severity,[87] the efficacy of lithium carbonate was confirmed in other studies in a high proportion of patients with both ECH and CCH.[88] Administration of 300 mg of lithium three times a day would be comparable in terms of reduction in headache intensity and in analgesic consumption to verapamil. In clinical practice, lithium carbonate is less manageable than verapamil because of a longer time to reach the complete pharmacologic effect and of a narrow therapeutic window.[79] However, it remains a useful therapeutic strategy.[7]

With regard to the mechanism of action, much is known about the effect of lithium in mood disorders, but very little in CH. In bipolar disorder, lithium carbonate was indeed shown to influence the concentrations of glutamate at the synaptic level, increasing the availability of this excitatory neurotransmitter viaN-methyl d-aspartate (NMDA) receptor stimulation[89] and by inhibition of its uptake via specific transporters.[90] Chronic lithium administration thus restores glutamate uptake (decreased in depression) to physiologic levels, exerting a mood-stabilizing function. Lithium also acts by increasing the concentrations of dopamine (DA) and γ-aminobutyric acid (GABA), contrasting depression on one side and mania on the other.[91] Finally, another accepted mode of action is the depletion of inositol, a sugar involved in maintaining phospholipid concentrations of cell membranes and the efficiency of cellular signaling. According to this hypothesis, lithium would act by controlling the inositol in excess.[92] All these findings are relevant to the pharmacology of mood disorders but have limited significance in the case of CH pathophysiology. However, the hypothalamus is generally considered as the central generator of the attacks in CH, and the accumulation of lithium in the hypothalamus of treated animals indicates this brain region as an important therapeutic target.[93]

The narrow therapeutic window puts the patients treated with lithium at risk of drug toxicity. For this reason, in the clinical setting, it is good practice to periodically control the serum lithium levels together with the electrolytes, the kidney function, and the thyroid function. The most frequent adverse events of lithium include tremor, gastrointestinal disturbances, dizziness, and polyuria.

Second-Line Treatments. Many other drugs were shown to be reliable in the long-term treatment of CH, even if with lower statistical significance. In cases in which the first-line treatments verapamil and lithium were not found effective or well tolerated by the patient, the drugs listed below represent an additional therapeutic chance when administered in both mono- and polytherapy.

Anti-epileptic Drugs. Following the evidence of their efficacy in the prevention of migraine, anti-epileptic drugs (AEDs) were also evaluated as preventive therapies in CH with encouraging results. Topiramate is considered as a second-line therapy.[7] In two open studies, different dosages (ranging from 25 mg to 200 mg/day) led the patient to clinical remission within about 3 weeks, interrupting or reducing the duration of the cluster period.[94,95] The most frequently reported side effects are weight loss, cognitive dysfunction, paresthesias, and the risk of recurrent stones in patients with a positive history for nephrolithiasis or cholelithiasis. Valproic acid was also found to be effective at doses of 500 to 2,000 mg daily in an o pen study[96] and is currently considered by the guidelines as a third-line therapy in CH.[7] In clinical practice, however, there are some

points to be kept in mind in order to avoid toxic effects. It is very important to measure the drug blood levels and monitor the liver function for the potential risk of hepatic failure. Reported adverse effects include weight gain, tremor, hair loss, and nausea. Gabapentin at doses of 800 to 3,600 mg/day was able to interrupt the cluster period in at least 50% of treated patients and to reduce significantly the frequency and intensity of the pain attacks in many others.[97–99] Rare reported side effects include somnolence, dizziness, and ataxia.

Serotonin Antagonists. Methysergide was consistently found to be effective in a high proportion of CH patients at doses of 8 to 16 mg/day,[100,101] but generally unadvised by many clinicians for two reasons: first, it was reported to produce pulmonary and retroperitoneal fibrosis in the long term unless periodically suspended;[102] in addition, it may create problems of management due to the frequent interactions with triptans. However, this drug is no longer available nearly anywhere in the world. For these reasons, other drugs of this class, like pizotifen, found their space. Pizotifen was shown to be effective in reducing attack frequency in 36% and in interrupting the cluster in 21% of patients treated with a dose of 1 to 4 mg/day.[103]

Other Treatments

Histamine sulphate, administered intravenously in patients with intractable CH, led to a complete remission of attacks in one-third of cases and a 50% reduction of attack frequency in another one-third.[104] In an RCT in 20 patients with ECH, a dose of 10 mg/day of melatonin was shown to induce a significant and relatively rapid reduction of headache frequency within 2 weeks of treatment.[105]

Clonidine, given as a 5- to 7.5-mg transdermal patch, gave positive results in both ECH and CCH patients, with reduction in frequency, pain intensity, and attack duration.[106] Tiredness and decreased blood pressure levels are common drug effects.

Baclofen (10 mg three times daily orally) was found in an open study to induce remission in most CH patients without significant side effects.[107]

Capsaicin, a derivative of homovanillic acid found in hot peppers, causes desensitization by depleting the nerve terminals of substance P and CGRP.[108] In ECH and CCH patients, repeated intranasal capsaicin application was found to be effective on the frequency of CH attacks when administered at a dose of 300 µg, both bilaterally[109] and only in the nostril ipsilateral to pain.[110] However, in CCH patients, the drug efficacy was limited in time, with a headache-free period not over 40 days.

Following evidence obtained in migraine, botulinum toxin type A was evaluated as add-on therapy also in ECH and CCH patients. However, the results obtained by injection of a cumulative dose of 50 UI in the pericranial muscles ipsilateral to the pain were inconsistent.[111] Further data are thus needed.

Given the high efficacy of triptans in the treatment of acute attack of CH, some authors suggested their possible use also as preventive therapy. Triptans with a medium and long half-life were indeed shown to be useful in the long-term prophylaxis of CH alongside the first-line treatment. In open studies, naratriptan and eletriptan were shown to be helpful and well tolerated as additional therapies in either long-term or transitional prophylaxis.[112,113] Frovatriptan, the triptan with the longest half-life (26 hours), was shown to be effective and safe at a dose of 5 mg/day in CH patients transitioning into longer term preventive therapy.[114] However, these data need to be confirmed in wider controlled studies. In the meantime, triptans can be reasonably used in the preventive management of CH as a second-line, short-term, bridging monotherapy or as add-on treatment in complicated cases.[115]

Civamide is a cis-isomer of capsaicin and, similarly to what was reported for capsaicin, causes the release and the subsequent depletion of neuropeptides (substance P and CGRP) in peripheral neurons, mainly in the type C nociceptive fibers. The reduction of the activity of type C fibers is in turn responsible for a process of desensitization that is exploited in the treatment of CH.[116] Intranasal civamide was indeed found to decrease the frequency of the CH attacks by more than 50% despite the few local adverse effects such as nasal burning, lacrimation, pharyngitis, and rhinorrhea.

In a controlled study, low-intensity anticoagulation with warfarin was associated with significantly higher incidence of remission and less impact of headache on refractory CH patients' lives compared to placebo.[117] In an uncontrolled study, the non-hallucinogen 2-bromo-lysergic acid diethylamide was found to either break a CH cycle or considerably improve the frequency and intensity of attacks in a case series.[118]

Ketamine as an intravenous infusion (0.5 mg/kg over 2 hours) combined with magnesium sulfate (3,000 mg over 30 minutes) was reported to induce sustained relief (6 months) in two patients with chronic intractable CH.[119]

CGRP Antagonists. CGRP is a potent vasodilating agent with a crucial role in pain transmission, particularly in trigeminal primary neurons. Intravenous infusion of CGRP with concomitant headache precipitation modulates the blood oxygen–level dependent (BOLD) signal in the brain of healthy subjects evoked by noxious heat stimuli of the trigeminal nerve.[120] This is in line with early observations that CGRP plasma levels increase in the external jugular vein blood on

the painful side during spontaneous CH attacks[121] and that high dose corticosteroids decrease CGRP release during the active period.[122] The exact mechanisms of this CGRP-mediated pain induction are still unclear, but a direct role appears to be unlikely.[123] Rather, CGRP may be involved in inducing peripheral sensitization with allodynia via activation of glial cells and stimulation of NO release, thus leading to inflammatory events in the tissue.[124] All these mechanisms may also explain the allodynic effects reported in CH patients.[125] Monoclonal antibodies (mAbs) targeting the free CGRP peptide[126] or the CGRP receptor[127] have been recently developed and investigated. They are characterized by elevated specificity, long half-lives, and a good tolerability profile. CGRP mAbs have been found to be effective in migraine sufferers, but they may also be beneficial in CH patients.[128] In this respect, there are currently studies investigating CGRP mAbs in both episodic and chronic CH.

Occipital Nerve Blocks. There is robust evidence that great occipital nerve (GON) blocks with steroids are beneficial as a transitional therapy in either episodic CH patients during the active phase or in refractory chronic CH patients, at variance with injection of simple anesthetics, which appear to be ineffective alone.[129] In a randomized placebo-controlled study in episodic CH patients in the active phase and chronic patients, the injection of a combination of long-acting betamethasone dipropionate, fast-acting betamethasone disodium phosphate, and lidocaine was found to induce a remission of at least 1 week in 85% of patients.[130] In another controlled study, suboccipital injections of cortivazol in episodic and chronic CH patients were observed to induce a > 50% decrease in attacks compared to the placebo group, with 76% of cortivazol-treated patients showing remission.[131] Among primary headaches, CH appears to respond most favorably to GON blocks,[129] and this treatment should be considered also for its tolerability and safety.

Neurostimulatory Techniques

Neurostimulation is a promising tool for the treatment of some idiopathic headaches refractory to the usual pharmacologic therapies. It is a field of current active research, and its role in the clinical management of CH has become increasingly important over the last years, particularly in the treatment of intractable CCH. Neurostimulation procedures for the treatment of intractable CH such as sensory rhizotomy, radiofrequency gangliorhizolysis, and microvascular decompression were developed following the failure of surgical approaches. These techniques have provided promising results. Four principal techniques are presently under investigation: deep brain stimulation (DBS) of the hypothalamus, occipital nerve stimulation (ONS), sphenopalatine ganglion (SPG) stimulation, and vagal nerve stimulation.

Deep Brain Stimulation of the Hypothalamus. This technique was introduced several years ago for refractory cases of chronic CH and showed reasonably good results, with an overall reduction in headache frequency ≥ 50% in over 65% of patients.[132] However, any improvement apparently takes several weeks of stimulation to become observable, and the only placebo-controlled trial on this procedure in CH patients reported a follow-up period of only 1 month.[132] In addition, studies were burdened with numerous adverse effects.[133,134] The reason chronic hypothalamic stimulation is effective is unclear, but a mechanism limited to the stimulated area would probably be insufficient. Among the proposed mechanisms of action are modulatory effects on the antinociceptive system by activation of the trigeminal nucleus and ganglion, an increased blood supply to pain-related brain regions (pain matrix), and a restored parasympathetic signaling in the superior salivatory nucleus.[135] However, new data are needed to confirm these observations and to clearly establish what characteristics the patient must have to be addressed by this treatment.

Occipital Nerve Stimulation. ONS is a relatively invasive technique that has been found to be effective in the long-term prevention of refractory chronic CH by several open studies, with a reported decrease of nearly 70%.[133,134,136] It has been recently pointed out that in CH this technique may be more effective than in chronic migraine and that the presence of mood/anxiety disorders at the time of implantation is associated with poorer response.[137] In addition to reducing the attack frequency, ONS has been reported to alleviate the functional and emotional headache impacts in refractory chronic CH patients and to significantly improve the health-related quality of life of responders.[138] The use of ONS, currently limited to drug refractory CH cases, is regulated by definite criteria issued by the European Headache Society.[139]

Sphenopalatine Ganglion Stimulation. SPG neurostimulation is a technique that should be initiated only in the case of failure of any previous treatment and in CH cases characterized by strictly unilateral pain.[140] Some open studies have indeed demonstrated a good clinical response in about 50% of CH patients; the frequency of responders appears to be even higher when SPG is used as acute treatment for ongoing pain attacks.[141,142]

Vagal Nerve Stimulation. Noninvasive stimulation of the cervical branch of the vagus nerve (nVNS) is a new technique that may help avoid the need for surgical implantation of a stimulator and reduce costs and morbidity. Human and animal studies have demonstrated that nVNS indeed activates vagus

nerve fibers similar to those implicated in the clinical benefits of invasive VNS. In open-label randomized studies, VNS was evaluated as an adjunctive prophylactic strategy in CH patients and was found to be effective and safe.[143] In another open-label study, nVNS (gammaCore) was investigated as acute treatment and reported to be effective in up to 47% of cases.[144] Recently, nVNS was found to be superior to sham therapy in episodic CH but not in chronic CH, confirming previous findings regarding its efficacy, safety, and tolerability.[145] The gammaCore device has been recently cleared by the FDA for the acute treatment of pain in episodic CH patients.

Treatment of Other TACs

It is difficult to evaluate the efficacy or establish the level of evidence of a treatment in the other TACs; ie, PH, HC, and SUNCT. Indeed, the shortness of the single acute attack makes it almost impossible to understand if the relief or the remission observed are drug-induced or spontaneous. Moreover, a high number of attacks per day requests the use of a preventive treatment rather than an exclusively symptomatic treatment. One further problem is that the low prevalence of TACs and the limited number of tested patients make it difficult to obtain statistically significant evidence.

PH and HC

Patients with PH or HC characteristically show an excellent response to indomethacin, so this particular feature has been introduced to the diagnostic criteria.[3] In cases in which effective doses of indomethacin (200 to 225 mg) do not produce any response or produce only a mild response, the diagnosis of PH or HC should be reconsidered.[146,147] The reason for this prompt response is still unknown, but functional imaging studies have provided some possible explanations: in addition to the activation in the posterior hypothalamus (common in most TACs), these syndromes also show activation in the ventral midbrain,[148] which could represent the potential target of indomethacin. Unfortunately, the treatment of PH and HC has so far been investigated only in open and noncontrolled studies; therefore, no reliable information is available about the required doses and the duration of treatment. However, it is suggested to start with a dose of indomethacin of 25 mg three times per day for 3 days that can be increased by 25 mg every 3 days. A complete therapeutic response is generally expected within 24 to 48 hours for a dose of 150 mg a day. As mentioned above, an unsatisfactory response to therapeutic doses of indomethacin should rule out the diagnosis or suggest a symptomatic form of PH and HC.[149] In patients with EPH or with remitting forms of HC, indomethacin at effective doses should be continued for a time longer than typical attack periods and then gradually tapered, while CPH and nonremitting HC often need long-lasting treatment. The continued intake of indomethacin puts the patients at risk of developing peptic ulcers and other gastrointestinal disorders. For this reason, it is always good practice to include in the treatment a proton pump inhibitor or H2 receptor antagonist.

Other nonsteroidal anti-inflammatory drugs (NSAIDs) were reported to be effective in TACs. Some evidence suggests that cyclooxygenase (COX)-2 selective inhibitors, such as rofecoxib and celecoxib, are effective in the treatment of PH, despite the increased risk of myocardial infarction and stroke associated with their prolonged use.[150–154] Moreover, a combination of piroxicam and β-cyclodestrine was reported to alleviate the clinical symptoms in both CPH and HC patients.[155] Finally, good results were also obtained with melatonin in HC patients[120] and with verapamil and topiramate in PH patients.[156] Prolonged relief was reported by the blockade of GON with local injection of steroids and lidocaine in one study in PH patients.[157]

SUNCT

As mentioned at the beginning of this section, the shortness of acute attacks, in particular in SUNCT and SUNA, makes any symptomatic attempt completely in vain. A correct approach should aim at interrupting and preventing the attacks. Though pharmacologic studies are difficult in SUNCT because of the small number of patients, clinical evidence based on anecdotal observations and case reports is presently available. However, the preventive treatment of these syndromes is mainly based on the use of AEDs. Although controlled studies are lacking, lamotrigine is the most studied and most prescribed drug in the short- and long-lasting treatment of SUNCT due to its efficacy coupled with notable safety and tolerability. Doses of 100 to 400 mg/day are considered effective, resulting in a significant improvement of pain and autonomic symptoms.[158–163] Lamotrigine must be titrated up to the effective dose very slowly due to the risk of severe adverse effects, mostly involving the skin (such as Stevens-Johnson syndrome). Carbamazepine at doses of 200 to 2,000 mg/day[164–170] and topiramate at doses of 50 to 200 mg/day[171–173] were reported to induce significant pain relief in a significant number of patients. Moreover, gabapentin alone at doses of 800 to 2,700 mg/day[174,175] or 400 mg in combination with oxcarbazepine 600 mg/day[176] appears to be effective in the long-term treatment of patients with SUNA (response 60%) or with SUNCT (45%). In single cases or in restricted groups of patients some effects have

been observed using verapamil,[177] intravenous or oral steroids,[178,179] or intravenous lidocaine.[180]

In an open label study in patients with medically intractable SUNCT and SUNA, occipital nerve stimulation was found to improve pain symptoms.[181] It was concluded than ONS may offer an effective and safe treatment option also in these disabling conditions.

In general, the problems with selection of patients and subsequent treatment make it difficult to evaluate reliably the success or failure of a given treatment.

Conclusions

TACs are a family of idiopathic headaches characterized by strictly unilateral pain, autonomic symptoms (parasympathetic and sympathetic), and severe disability that reduces the quality of life of affected patients. Much is already known about the pathophysiology of these syndromes (Fig 1), but there is much to discover.[182] The involvement of the posterior hypothalamus, as suggested by the circadian pattern of the attacks and by the seasonal occurrence of cluster periods and confirmed by neuroimaging, draws attention to the deregulation of central pain pathways as an important etiopathogenetic moment. Due to the release of CGRP and substance P, neuroinflammatories are still today the principal therapeutic target of most available drugs. Unfortunately, their clinical efficacy and tolerability are supported only by a limited number of RCTs, some open studies in small case series, and single case reports. With these limitations, triptans and oxygen for acute attacks, steroids in transitional prophylaxis, and verapamil and lithium in prevention remain the elective treatments in CH. Indomethacin is extremely effective in PH and HC, while anti-epileptic drugs, especially lamotrigine, appear to be increasingly useful in SUNCT. Invasive interventions at the level of GON have shown to be effective in CH, and while DBS may be beneficial in selected cases, neurostimulation appears to be particularly promising in the same patients.

Further data are needed to elucidate the pathophysiologic mechanisms of TACs and identify new potential therapeutic targets. New large randomized and controlled clinical studies must be designed to evaluate novel treatments with the aim of strengthening the current levels of evidence and improving patients' quality of life in these highly disabling conditions.

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