

## Diagnosis, symptomatic therapy and preventive therapy of cluster headache

### Introduction

The term *cluster headache* (CH) was introduced for the first time in 1952 by Kunkle et al. [1] who underscored, with the term *cluster*, one of the principal characteristics of this particular form of headache, i.e. occurrence of attacks in clusters. However, CH was certainly already known in the 1930s, when Horton et al. [2] clearly described this headache form in a broad patient population, and, perhaps even earlier, under different terms [3–6].

The few epidemiological studies in the literature carried out on the general population indicate a prevalence of CH of around 0.1% [7, 8]. CH clearly predominates in males [9–12], even if in the cases with onset beginning from the 1980s onward, a clear male predominance appears to have decreased [13, 14]. The average age at onset of CH is 29–30 years of age, but an onset after 50 years of age is possible and also, although rare, an onset in childhood may not be excluded [9–12].

Despite the fact that the clinical picture of CH is extremely typical, past cases of CH were underestimated because many patients with this form of headache were misdiagnosed as having trigeminal neuralgia, sinusitis or dental disease. The diffusion and general acceptance of the International Headache Society's classification [15] have led to specific and precise clinical criteria necessary for the diagnosis of the individual headache forms. This has led, fortunately, to a reduction in misdiagnoses of CH in clinical practice.

### Diagnosis

Cluster headache is easy to diagnose because it is distinguished by attacks that present clear and specific clinical characteristics. The attacks tend to recur over time with features which remain constant, both in the same patient and between different patients.

The diagnosis of CH is founded essentially on the history of the patient, and clinical information should be carefully collected in detail. The questions for the patient and the subsequent clinical history which emerge should be focused not only on the clinical characteristics of the individual attacks but also on the way they recur over time.

For the diagnosis of individual attacks, it is advisable to use a semistructured interview based on the diagnostic criteria of the IHS [15].

- A. At least 5 attacks, fulfilling criteria B-D of the IHS classification for CH.
- B. Severe, unilateral pain, with orbital, supraorbital and/or temporal location, lasting from 15 to 180 minutes (without treatment).

Pain in CH is of a particularly severe intensity. Using a visual analogical scale, 87% of the patients indicated that the maximum pain intensity experienced during the attack was scored between 8 and 10 centimeters on the scale, with an average score of 9.17 [16]. CH is, by definition, headache with a strictly unilateral distribution. Even though cases with a bilateral location of pain have been described, they are sporadic, not exceeding 1%–2% of a broad and diverse CH patient population [9–12].

In addition to those cranial-facial areas affected by pain, as indicated in the diagnostic criteria of the IHS classification, other locations not infrequently involved are in the occipital and frontal regions (and not only supraorbital area) [17]. It is also advisable to ask the patient if pain is felt in the zygomatic and dental regions. This finding can be an additional element supporting the diagnosis [11].

The duration of a spontaneous CH attack can exceed 3 hours but only occasionally, and in a limited number of patients.

- C. Headache associated with at least one of the following 8 signs ipsilateral to the pain:
  1. Conjunctival injection
  2. Lacrimation

3. Nasal congestion
4. Rhinorrhea
5. Facial perspiration
6. Miosis
7. Ptosis
8. Eyelid edema

Subsequent to the publication of the IHS classification [15], careful revision of a large number of CH patients identified cases of CH without associated symptoms [18, 19]. However, the elimination of this criterion could run the risk of overestimating the number of cases of CH.

During a CH attack, a clear majority of patients display a characteristic behavior: they cannot stay still, they seem restless, they must keep moving and pace back and forth [10, 11, 16]. Psychomotor agitation could be considered to be a possible ninth factor associated with pain. The inclusion of this additional factor in the diagnosis of CH may help account for some cases which otherwise would not have been considered [17]. It is therefore advisable, while gathering the medical history, to inquire about the patient's behavior during the attack.

Of the eight associated signs, those with the better sensitivity and specificity indexes are lacrimation, nasal congestion and rhinorrhea, all ipsilateral to the pain. Although ptosis and miosis ipsilateral to the pain have a good specificity, they are not easily perceived by the patient, and consequently there is little chance of them being reported not even during a thorough patient history write up.

- D. Attack frequency is between 1 attack every 2 days and 8 attacks daily. The CH attacks occur, in the majority of cases, 1–3 times per day. Attacks lasting a relatively long time (2–3 hours) have a lower rate of recurrence (once every 1–2 days). It is useful to ask patients if their crises manifest themselves at particular times, keeping in mind that there are certain times of the day (e.g. 2–3 p.m., 9–10 p.m.) and of the night (e.g. 1–2 a.m. or, however, in relation to the first REM phase of sleep) in which the possibility of an attack is greater [11, 20].
- E. The clinical history, the general and neurological examinations, and eventual laboratory, neurophysiological and imaging testing exclude an organic cause of the headache under study.

As more unusual elements emerge from the clinical history, it is advisable to think of a possible underlying organic condition. It therefore becomes essential to carry out a thorough general and neurological examination and, if necessary, to resort to appropriate and specific testing. Dozens of patients have been described since the late 1970s who were considered to be symptomatic cases of CH [21]. For some of these cases, however, the clinical characteristics of the headache have not been reported in detail or those

described do not correspond to CH. For the others, the follow-up, after the exclusion of organic pathologies, is not enough to eliminate the doubt between a causal role and a simple concomitance. The possibility remains, however, although remote, that a cerebral organic pathology (e.g. arteriovenous malformations, aneurysms, hypophyseal expansive processes) or cervical pathology (e.g. meningiomas, aspergillomas) produces head pain similar to that of CH. Neuroradiological investigations should, however, be considered in particular cases even in the absence of specific indications, for example, in those patients who are excessively worried that they may have a serious, organic pathology underlying their headache.

The accurate gathering of the clinical history distinguishes two principal subtypes of CH that may be differentiated on the basis of their different *temporal pattern*: episodic CH (around 90% of the total cases of CH) and chronic CH (around 10% of the cases).

#### Diagnosis of episodic CH

The following criteria are the same as those indicated in the IHS classification level [15]:

- All the criteria listed for the diagnosis of CH should be fulfilled.
- At least 2 active headache periods (clusters) lasting from 7 days to 1 year (without treatment), separated by remission periods of at least 14 days.
- In the majority of the cases the active period lasts 1–2 months and the alternating remission period lasts from a few months to 2 years. Active periods may rarely occur for less than a week, the so-called mini-clusters [22].
- At the beginning of an active period, the attack frequency may be less than the minimum time limit (1/2 day) indicated in the IHS diagnostic criteria [15].

#### Diagnosis of chronic CH

The following criteria are the same reported in the IHS classification [15]:

- All the criteria reported for the diagnosis of CH must be fulfilled.
- Absence of remission periods, or remission periods lasting less than 14 days, for at least one year.

The absence of interval phases without headache may characterize CH from its onset (primary chronic CH) or may intervene more or less after a long history of episodic CH (secondary chronic CH).

### Further elements

The patient should be questioned about personal behavioral choices, in particular cigarette smoking. In fact, over 80% of patients with CH smoke, and more than half of smokers with CH smoke more than 20 cigarettes per day [10, 11, 23]. It is also advisable to ask the patient if he has succeeded in identifying possible trigger factors for the single attacks, with particular attention to the consumption of alcoholic drinks.

In the past, in the cases in which the diagnosis of CH was in doubt, pharmacological induction tests were carried out with vasodilatory substances, such as nitroglycerin [24] and histamine [25, 26]. With these substances, the attack may be triggered during the active period of CH, but not in the interval phase of remission. The test with nitroglycerin (1 mg by sublingual route) shows an appreciable sensitivity but a scarce specificity, while the test with histamine (0.3–0.5 mg by subcutaneous route) appears to be burdened by strongly conflicting results [25–27]. Of the two induction tests, the one with nitroglycerin is also used today for research purposes to study CH attack, since it is not easy for a researcher to investigate a spontaneous CH crisis.

Since the diagnosis of CH does not present particular difficulties if the clinical history is complete and accurate, it is not necessary to use pharmacological induction tests for diagnostic purposes.

### General examination

The general physical examination, carried out at the first visit for a headache, should include at least the following elements: vital signs (arterial pressure and heart rate), cardiac status, extracranial (paranasal sinuses, extracranial arteries, paraspinal cervical muscles and temporomandibular articulations) and cervical motility.

A neurological examination should be carried out, evaluating in particular: the ocular fundi, pupillary size and reactivity, extrinsic ocular motility, the eyelids, sensitivity in the area of innervation of the fifth cranial nerve and the corneal reflex.

### Laboratory and neurophysiological testing, and imaging

Abnormal findings at the general examination unusual in CH suggest that neuroradiological investigations be carried out. An exception is possible bradycardia and a partial Bernard-Horner sign, ipsilateral to the pain. It should be remembered that MRI may be more sensitive than CT in revealing abnormalities of irrelevant clinical significance, but not more sensitive in identifying clinically significant abnormalities.

Many studies have been carried out during the past decades, with the purpose of clarifying the pathophysiological mechanisms of CH and, on the basis of these results, different etiopathogenetic hypotheses have been formulated. Interesting findings have concerned the carotid circulation [28], neurovegetative [29–32] and neuroendocrine functions [33–39], the immune system [40–42], neurophysiological [43, 44] and biochemical [45, 46] aspects, as well as the trigeminovascular system [47, 48]. In the last few years, sophisticated neuroimaging techniques (e.g. positron emission tomography) have shown hypothalamic activation during a CH attack induced by nitroglycerin [49] and, more recently, a stable structural alteration of the posterior hypothalamus [50].

Unfortunately, however, until now notable progress in the knowledge of the inner mechanisms underlying CH has not been confirmed through instrumental examinations which may be potentially applied for diagnostic purposes. There is no evidence to support the use of electroencephalography [51], transcranial Doppler [52], CT [53] or MRI [54, 55] in the diagnosis of CH. Neuroradiological investigations should be avoided if they do not allow for variations in the therapeutic approach and are not recommended if the patient is not more likely to present significant abnormalities compared to the general population.

### Level of evidence, strength of evidence and recommendations for CH diagnosis

For the diagnosis of individual attacks the members of the Ad Hoc Committee assigned a level of evidence D, a strength of evidence + and recommendation II. The use of pharmacological induction tests for diagnostic purposes was judged as having a strength of evidence ++ and recommendation III. Both general and neurological examinations received a level of evidence D, strength of evidence +, and recommendation I. Neurological investigations, even in the absence of specific indications, received a strength of evidence + and recommendation III, when patients thought that a serious pathology was responsible for CH. A strength of evidence + was attributed to the need of a neuroradiological investigation in the case of abnormal findings at general examination.

### Symptomatic treatment

The objectives of symptomatic therapy for CH are the following:

- Treat the attack at the onset;
- Promote resolution and significant relief of pain and associated vegetative phenomena;

- Obtain this result in the shortest time (within 15 minutes after initiating treatment)
- Minimize side effects.

### Sumatriptan

Sumatriptan belongs to the pharmacological class of triptans. Two clinical trials, controlled versus placebo, investigated the effectiveness of this molecule in relieving a CH crisis [56, 57]. The significant effectiveness of subcutaneously administered sumatriptan found in these studies has been confirmed by the clinical experience of the members of the Ad Hoc Committee. The drug was used by subcutaneous route at a dose of 6 mg. As indicated in the chapter “Symptomatic treatment of migraine”, the side effects are certainly more numerous than those occurring with placebo, but they are generally of slight or moderate entity. The most common side effect is transitory pain at the injection site. Other collateral effects reported include pain, tingling, and sensations of warmth, heaviness, pressure or tightness. These symptoms, defined as “triptan symptoms”, are transitory and may involve any part of the body, including the chest and throat. The members of the Ad Hoc Committee believe that these symptoms, when present, are milder than those observed in patients with migraine. Such characteristics render subcutaneously administered sumatriptan the first-choice drug for the symptomatic treatment of CH.

Observational studies have confirmed the effectiveness of sumatriptan in treating multiple attacks over time, with a good safety profile [58, 59]. Indications from the Italian Ministry of Health foresee that this formulation should not be taken more than 2 times per day, with at least one hour between doses, even if data in the literature point out that dosages up to 3–4 times per day do not induce additional or particularly severe side effects [60]. Another observational study has also shown the effectiveness of sumatriptan on the accompanying vegetative symptoms [61]. Nasal congestion, rhinorrhea, lacrimation and photophobia generally disappear with the pain, while conjunctival hyperemia, miosis and ptosis resolve a little later.

Particular attention should be noted regarding the association of sumatriptan with drugs containing ergotamine for the possible appearance of prolonged vasospastic reactions. Sumatriptan should not be taken within 24 hours after administration of an ergot derivative. Conversely, ergot-containing medication should not be used within 6 hours after administration of sumatriptan.

The efficacy of sumatriptan nasal spray, at the dosage of 20 mg, has been investigated in only 1 open controlled study, in comparison to the 6-mg subcutaneous formulation

[62]. The results indicate a lower efficacy of sumatriptan nasal spray compared to subcutaneously given sumatriptan. The side effects are not severe, but are of light intensity and are infrequent.

Sumatriptan nasal spray, at the dosage of 20 mg, may be taken only two times in the same day, and in any case not within 2 hours of the first dose. The contraindications and pharmacological interactions are the same as for the subcutaneous formulation. The majority of the members of the Ad Hoc Committee have not enough experience to express a judgement of therapeutical efficacy of nasal spray formulation.

### Zolmitriptan

Only one controlled clinical trial versus placebo has been reported [63]. The primary end point was the reduction of pain intensity by at least 2 points on a verbal scale from 0 to 4 in 30 minutes; the drug at the dosage of 10 mg, per os, appeared to be efficacious only in episodic cluster headache. The members of the Ad Hoc Committee believe that the drug tested at 5 mg is inefficacious.

The dosage of 10 mg exceeds the maximum level recommended (5 mg) by the Italian Health Ministry.

### Oxygen by inhalation

There is only one clinical trial [64] and one open study [65] in the literature on the use of inhalatory oxygen in CH. Oxygen, at 100%, is administered for 15 min with a facial mask at a rate of 6–7 l/min. These studies concur in attributing a high level of evidence to this therapeutic intervention. The members of the Ad Hoc Committee, on the basis of their clinical impression, also expressed a positive consensus on its effectiveness. The drug may therefore be considered a valid second-choice therapeutic option in cases in which there are contraindications to the use of sumatriptan, or if the daily crises are numerous, while waiting for the beneficial effect from a prophylactic treatment.

Today the possibility of having gaseous or liquid oxygen at home presents no particular problems since this gas is available in any pharmacy. After oxygen use, a new unexpected crisis of CH may recur.

There is only one controlled clinical trial of hyperbaric oxygen therapy versus placebo [66] and two observational studies [67, 68]. This therapy is generally carried out by administering 100% O<sub>2</sub> for 30 minutes, in a hyperbaric chamber at 2 atmospheres pressure. A shorter duration of crises has been reported in treated patients compared to those treated

with placebo [66]. The results do not reach, however, a clear statistical significance. No side effects have been reported. The members of the Ad Hoc Committee could not express an evaluation of the clinical efficacy of this procedure.

The administration of hyperbaric oxygen is a difficult procedure to carry out; a hyperbaric chamber should be available at the moment of the onset of the crisis.

#### Ergotamine in association with caffeine

Clinical research on the use of ergotamine in the symptomatic treatment of CH, at least in the preparations available in Italy, was carried out many years ago. In these open studies the effectiveness of the association between ergotamine and caffeine, both in tablets (1 mg ergotamine + 100 mg caffeine) [69] and suppositories (2 mg ergotamine + 100 mg caffeine), was tested [70]. The results do not demonstrate a clear effectiveness of these associations and the members of the Ad Hoc Committee, on the basis of their personal clinical experience, did not judge these drugs, in these combinations, to be active in the treatment of a CH attack. The association between ergotamine and caffeine in their different formulations was, therefore, not recommended in the symptomatic treatment of CH.

#### Dihydroergotamine

Only one placebo-controlled clinical trial has been carried out, which investigated the effectiveness of dihydroergotamine in the nasal spray formulation at a dose of 0.5 mg per spray per nostril in the attack of CH [71]. In this study, dihydroergotamine was not able to stop the CH crisis, but only to reduce the intensity of the symptoms. On the basis of their clinical experience, the members of the Ad Hoc Committee considered this molecule to be completely ineffective in this formulation. The dihydroergotamine nasal spray was, therefore, not recommended in the symptomatic treatment of CH.

#### Lidocaine

Only two uncontrolled open studies have been carried out [72, 73]. In the first [72], 1 ml of a 4% lidocaine solution (40 mg) was instilled in the nostril, ipsilaterally to the pain. All the treated attacks were, however, provoked by the administration of nitroglycerin. In the second study [73], 4% lidocaine in the nasal spray formulation was administered, 4 sprays immediately and another 2 after 15 min (however the dose of the drug administered per spray was not defined).

The data that emerged from these two studies do not provide definite clinical evidence of effectiveness, considering the fact that the first study [72] did not refer to spontaneous CH attacks. The members of the Ad Hoc Committee believe, on the basis of their clinical evaluation, that this drug is ineffective. Lidocaine is therefore not recommended for the symptomatic treatment of CH.

#### Prophylactic treatment

In the last few years important innovations have been introduced in the therapy of CH. The principal objectives of prophylactic therapy are to achieve the rapid disappearance of the attacks and consequently to end the cluster phase. Secondary objectives are aimed at reducing the frequency, the intensity and the duration of the attacks. Preventive treatment is judged effective and safe only in chronic CH, because in the recurrent and episodic CH forms there is always doubt that the crisis period resolves spontaneously rather than as a consequence of the established treatment. Accordingly, the principles of prophylactic treatment are:

- Begin treatment early, particularly in the episodic forms
  - Continue treatment for at least 10–14 days after the disappearance of the crises
  - Gradually suspend treatment
  - If the crises reappear, increase dosages to therapeutic levels
  - Begin treatment again with the onset of a subsequent cluster phase
- The drug choice depends on different factors:
- Age and lifestyle of the patient (eliminate alcohol and smoking during crisis periods)
  - Expected duration of the cluster phase
  - Type of CH (episodic or chronic)
  - Response to previous treatments
  - Possible reported side effects
  - Contraindications to the use of recommended drugs
  - Comorbid pathologies

#### Verapamil

Today, verapamil is considered the first-choice drug for the prophylactic treatment of CH, in both the episodic and chronic forms. The effectiveness of verapamil at the dosage of 360 mg/day, per os, has been demonstrated, and the drug is currently the most widely used [74, 75]. It is effective, in the majority of patients and with few side effects at higher doses. In an open study involving 48 patients, 69% reported an improvement greater than 75% during treatment with

verapamil [74]. In another recent study, double-blind versus placebo, the effectiveness of verapamil (360 mg/day) was investigated in 30 patients, for a period of 2 weeks. In the patients treated with verapamil (N=15), a statistically significant reduction in the frequency of the crises and in the use of analgesics was shown, which was more evident in the second week of treatment [75].

The initial dose of a delayed-release preparation is 120 mg, 3-times per day. Two-thirds of patients show an improvement greater than 50% with the daily dose of 240 mg.

Verapamil should be associated with lithium with caution in the most severe cases; otherwise, it is generally well tolerated and there are no interactions with sumatriptan, corticosteroids or other prophylactic drugs.

The most annoying side effect is constipation. An electrocardiogram is advisable before administering this drug to exclude an atrial-ventricular block.

It should be remembered that the drugs belonging to this category must be used with caution if administered together with  $\beta$ -blockers.

#### Prednisone

Prednisone is effective and has a rapid preventive action in the treatment of episodic CH. It should be considered a second-choice drug. In chronic CH the drug induces a rapid relief of the crises, and is useful in the early phase of treatment, when the preventive drugs are still not yet effective. The association prednisone + lithium was much more effective in a study of 56 patients affected by chronic CH followed for 3.2 years [76].

A large open study [77] showed a marked improvement in 77% of 77 patients suffering from episodic CH and a partial benefit in another 12%, both treated with prednisone administered per os.

Prednisone is used at doses of 50–60 mg/day for 2–3 days, decreasing the dose by 10 mg/day every 2–3 days.

Until side effects appear, this drug can be used only for inducing the remission of the most serious cases with high attack frequency and intensity, particularly in the central phase of the cluster.

Headache may reappear when the dose of prednisone is lowered to less than 25 mg/day. In this case, another first-choice prophylactic drug may be associated with prednisone.

The treatment period should not exceed 3 weeks.

#### Dexamethasone

In an open study [78] carried out on 15 patients with episodic CH, dexamethasone, parenterally administered, at a dose of 4 mg two times per day in the first two weeks, and then 4

mg per day the following week, was able to interrupt the cluster phase. The members of the Ad Hoc Committee could not express a judgement of efficacy.

#### Lithium

Lithium has been used in different psychiatric and medical pathologies, and is effective in the prophylaxis of both chronic and episodic CH. Today it is widely used in clinical practice, although only open clinical studies have been performed.

Overall, in 28 clinical studies involving 428 patients, satisfactory results have been obtained in 304 (78%) of the patients affected by chronic CH [79]. After the suspension of treatment, a shift from the chronic to the episodic form was demonstrated in this group of patients [79].

Even in a group of 164 patients affected by episodic CH, lithium has been shown to be effective, with a significant improvement observed in 63% of the patients [80]. A double-blind study, carried out in a group of 30 patients affected by chronic CH, compared verapamil (360 mg/day) and lithium (900 mg/day), and found an equal effectiveness of the two drugs, but fewer side effects and a shorter latency period with verapamil [81].

One double-blind clinical study versus placebo was unable to show a greater effectiveness of lithium (800 mg, delayed-release formulation) than placebo; this study was interrupted after 1 week of treatment and, unexpectedly, a response to placebo equal to 31% was noticed [82].

The initial dose is on average 300 mg, 3-times per day, while the maximum dose is generally 1200 mg/day. Effectiveness is seen after a few days of treatment (at dosages of 600–900 mg/day).

Lithium is effective at serum concentrations of 0.4–1.2 mEq/l, lower than those necessary for treatment of bipolar disorders. Serum levels should be measured 12 hours after the last dose, and should not exceed 1.2 mEq/l.

It is necessary to periodically measure serum lithium levels and to check for thyroid and renal functional parameters both before and during treatment. The most frequent side effects associated with lithium treatment are tremors, diarrhea, and mental confusion. It must be used with caution in association with calcium channel blockers, some selective serotonin-reuptake inhibitors (SSRIs), thiazide diuretics, indomethacin and diclofenac.

#### Melatonin

Serum and urinary levels of melatonin are reduced in patients affected by CH, particularly during the cluster phase [38, 83]. On the basis of these observations, the periodicity of CH and

the hypothalamic involvement in its pathogenesis, the effectiveness of the oral administration of 10 mg melatonin per os was demonstrated through a double-blind study versus placebo in 20 patients affected by episodic CH [84]. The remission phase was obtained in 3–5 days in half of the patients treated with melatonin, in contrast to CH patients treated with placebo.

#### Pizotifen

In the only single-blind study carried out on 28 patients suffering from episodic CH, the disappearance of the crises has been reported in 21% of patients and 36% showed an improvement of the crises greater than 50% [85]. The maintenance dose of pizotifen was 3 mg/day, which should be reached progressively.

#### Clonidine

Clonidine was used in only one open short-term study, in a group of 13 patients affected by CH (N=8 episodic form; N=5 chronic form) and was administered by transdermal route at doses of 5.0–7.5 mg/day for 1 week. It induced a 50% reduction of the frequency, duration and intensity of the crises [86].

In another open study, clonidine was administered by transdermal route for 2 weeks (5 mg/day the first week, 7.5 mg/day the second week), to 16 patients affected by episodic CH [87]. The disappearance of the crises, after 7 days of treatment, was noticed in only 5 of 16 patients examined.

The members of the Ad Hoc Committee were not able to express any judgement on the clinical efficacy of transdermal clonidine in chronic CH.

#### Valproic acid

In an open clinical study, valproic acid has been used for the treatment of 13 patients with episodic CH [88]. In 9 of these patients the disappearance of the crises was observed after 1–4 days of treatment, and the drug was, in any case, well tolerated. The dosage varied from 600 to 2000 mg/day, given in two doses. Even if the drug may cause several adverse effects, they are, however, infrequent [89]. They include: weight gain, temporary hair loss, gastrointestinal disturbances, sedation and cognitive impairment. These adverse effects tend to disappear with decreasing dosages. Valproic acid is contraindicated in pregnancy due to the potentially dangerous effects on the neuraltube and should also not be used when there are liver disturbances. While the drug may increase the serum levels of ben-

zodiazepines and barbiturates if contemporarily administered, these associations should be used carefully in clinical practice.

Monitoring of drug blood levels, hematic crisis and hepatic and pancreatic functional parameters is necessary.

The members of the Ad Hoc Committee could not express any judgement on the efficacy of the drug.

#### Topiramate

In a recent open study [90], an improvement of 10 patients affected by CH was demonstrated after the administration of 50–125 mg topiramate, fractioned in two daily doses. In nine patients the remission phase occurred after 2 weeks of treatment; two of them were affected by chronic CH. The dosage and the eventual adverse events were reduced when treatment began with low doses which were gradually increased. The adverse events reported are somnolence, stupor, ataxia, and cognitive disturbances.

The members of the Ad Hoc Committee could not express any judgement on the efficacy of the drug.

#### Capsaicin

In a double-blind study, capsaicin, at a concentration of 0.025%, applied 2-times per day for 7 days in the ipsilateral nostril, has been shown to be more efficacious than placebo in reducing the frequency and intensity of the crises [91]. The unpleasant local reactions induced by the drug make it difficult to manage in the long-term treatment of cluster headache. The patients affected by episodic CH seemed to have greater clinical benefit compared to those affected by the chronic form.

The drug, used in galenic form, is not available in Italy. Moreover, the members of the Ad Hoc Committee did not believe it necessary to express any judgement on the efficacy of this preparation.

#### Dihydroergotamine

Dihydroergotamine, intravenously administered, has been demonstrated to induce the rapid disappearance of cluster attacks when administered daily, for a short time period (0.5–0.8 mg in 8 h, until the disappearance of the crises) [92]. This retrospective study was carried out on 54 patients, of whom 23 had episodic CH and the remaining 31 had chronic CH. This drug is contraindicated in patients affected by peripheral vasculopathies, coronary disease and hypertension. It should not be associated with triptans.

Dihydroergotamine, formulated for intravenous administration, is not available in Italy.

### Methysergide

Methysergide is a semisynthetic ergot alkaloid. Old, open studies demonstrated that the drug is efficacious in 50%–70% of cases [93, 94]. According to the study of Curran et al. [95], which reviewed all the studies available in the literature before 1967, for a total of 451 patients, the percentage of the efficacy data was about 73%. On the contrary both Kudrow [10] (who only investigated patients with chronic CH) and Krabbe [96] found efficacy percentages ranging from 20% to 30%. The dosages varied from 4 to 10 mg/day. The drug, however, needs to be suspended for at

least two months after a treatment period of 4 months, due to the adverse effects of retroperitoneal, pleuropulmonary and endocardiac fibrosis.

The drug is no longer commercially available in Italy.

### Level of evidence, scientific strength of evidence, and assessment of clinical effectiveness

Drugs used in the symptomatic treatment of cluster headache are listed in Table 1, together with scores regarding evidence towards their use. Drugs used in the prophylaxis of episodic and chronic cluster headaches are given in Tables 2 and 3, respectively. The recommendation groups of drugs for the symptomatic and prophylactic treatments of cluster headache are shown in Tables 4 and 5, respectively.

**Table 1** Characteristics of drugs used in the symptomatic treatment of cluster headache

	Level of evidence	Scientific strength of evidence	Clinical effectiveness	Adverse events
Sumatriptan, 6 mg SC	A	+++	+++	Occasional, not severe
Sumatriptan, 20-mg nasal spray	C	++	?	Rare, not severe
Zolmitriptan, 10 mg per os	B	++	?	Occasional, not severe
Oxygen inhalation, 100% O <sub>2</sub> , 6–7 l/min for 15 min	B	++	++	Rare, not severe
Hyperbaric oxygen therapy, 100% O <sub>2</sub> for 30 min at 2 atm	B	+	?	Not reported
Ergotamine + caffeine, 1 mg + 100 mg per os	C	+	+	Occasional, not severe
Ergotamine + caffeine, 2 mg + 100 mg suppository	C	+	+	Occasional, not severe
Dihydroergotamine, 0.5 mg nasal spray	B	+	0	Occasional, not severe
Lidocaine, 4% solution applied intranasally	C	+	+	Occasional, severe
Valproic acid, 600–1200 mg/day per os	C	++	?	Occasional, not severe
Topiramate, 50–125 mg/day in 2 administrations	C	+	?	Frequent, not severe
Capsaicin, 0.025% solution applied intranasally bid, ipsilaterally to the pain <sup>a</sup>	C	++	?	Frequent, not severe
Dihydroergotamine, 0.5–1.0 mg in 8 h until crises end <sup>a</sup>	C	++	++	Frequent, not severe
Methysergide, 4–10 mg/day per os <sup>a</sup>	C	+	+	Rare, not severe

The efficacy dose tested is indicated after each drug  
SC, subcutaneously administered

<sup>a</sup> Not available in Italy

**Table 2** Characteristics of drugs used in the prophylaxis of episodic cluster headache

	Level of evidence	Scientific strength of evidence	Clinical effectiveness	Adverse events
Verapamil, 120 mg per os, bid or tid	B	+++	+++	Rare, not severe
Prednisone, 50–60 mg/day per os, tapering over a maximum of 3 weeks	C	+++	+++	Rare, not severe
Dexamethasone, 4 mg bid IM or IV for 2 weeks, then 4 mg/day for 1 week	C	++	?	Rare, not severe
Lithium, 30 mg per os, tid or qid	C	+++	+++	Rare, severe
Melatonin, 10 mg/day per os	B	++	?	Not reported
Pizotifen, 3 mg/day per os	B	++	?	Rare, not severe
Clonidine, 5.0–7.5 mg/day transdermally	C	+	0	Frequent, not severe

The efficacy dose tested is indicated after each drug

*IM*, intramuscularly; *IV*, intravenously; *bid*, 2 times a day; *tid*, 3 times a day; *qid*, 4 times a day

**Table 3** Characteristics of drugs used in the prophylaxis of chronic cluster headache

	Level of evidence	Scientific strength of evidence	Clinical effectiveness	Adverse events
Verapamil, 120 mg per os, bid or tid	C	+++	+++	Rare, not severe
Prednisone, 50–60 mg/day per os, tapering over a maximum of 3 weeks	C	++	?	Rare, not severe
Lithium, 300 mg per os, tid or qid	C	+++	+++	Rare, severe
Clonidine, 5.0–7.5 mg/day transdermally	C	++	?	Frequent, not severe
Capsaicin, 0.025% solution applied intranasally bid for 7 days, ipsilateral to the pain <sup>a</sup>	B	+	?	Frequent, not severe
Dihydroergotamine, 0.5–1.0 mg in 8 h until crises end	C	++	++	Frequent, severe
Methysergide, 4–10 mg/day per os	C	+	+	Rare, severe

The efficacy dose tested is indicated after each drug

<sup>a</sup> Not available in Italy

**Table 4** Recommendation groups of drugs for the symptomatic treatment of cluster headache

Group I	Group II	Group IIIa	Group IV
Sumatriptan, subcutaneously administered	Oxygen therapy (inhalatory)	Ergotamine + caffeine, per os Ergotamine + caffeine, suppository Lidocaine 4%, intranasally	Sumatriptan, nasal spray Zolmitriptan, per os Hyperbaric oxygen therapy Dihydroergotamine, nasal spray

**Table 5** Recommendation groups of drugs for the prophylaxis of episodic and chronic cluster headache (CH). No drugs fall into recommendation group I for cluster headache

	Group II	Group IIIa	Group IIIb	Group IV
Episodic CH	Verapamil, per os	Prednisone, per os	Lithium, per os Methysergide, per os	Dexamethasone, per os Melatonin, per os Pizotifen, per os Clonidine, transdermal route Valproic acid, per os Topiramate, per os Capsaicin, intranasal route Dihydroergotamine, intravenous route
Chronic CH	–	Verapamil, per os	Lithium, per os Methysergide, per os	Prednisone, per os Clonidine, transdermal route Capsaicin, intranasal route Dihydroergotamine, intravenous route

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