

EFNS TASK FORCE ARTICLE

EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias

A. May^a, M. Leone^b, J. Áfra^c, M. Linde^d, P. S. Sándor^e, S. Evers^f and P. J. Goadsby^g^aDepartment of Systems Neuroscience, University of Hamburg, Hamburg, Germany; ^bInstituto Neurologico Carlo Besta, Milan, Italy;^cNational Institute of Neurosurgery, Budapest, Hungary; ^dCephalea Pain Centre and Institute of Neuroscience and Physiology, Sahlgren Academy, Göteborg University, Göteborg, Sweden; ^eDepartment of Neurology, University of Zurich, Zurich, Switzerland; ^fDepartment of Neurology, University of Münster, Münster, Germany; and ^gInstitute of Neurology, Queen Square, London, UK**Keywords:**

cluster headache, paroxysmal hemicrania, SUNCT syndrome, treatment guideline, trigeminal-autonomic cephalalgias

Received 24 April 2006

Accepted 25 April 2006

Cluster headache and the other trigeminal-autonomic cephalalgias [paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome] are rare but very disabling conditions with a major impact on the patient's quality of life. The objective of this study was to give evidence-based recommendations for the treatment of these headache disorders based on a literature search and consensus amongst a panel of experts. All available medical reference systems were screened for any kind of studies on cluster headache, paroxysmal hemicrania and SUNCT syndrome. The findings in these studies were evaluated according to the recommendations of the European Federation of Neurological Societies resulting in level A, B or C recommendations and good practice points. For the acute treatment of cluster headache attacks, oxygen (100%) with a flow of at least 7 l/min over 15 min and 6 mg subcutaneous sumatriptan are drugs of first choice. Prophylaxis of cluster headache should be performed with verapamil at a daily dose of at least 240 mg (maximum dose depends on efficacy or tolerability). Although no class I or II trials are available, steroids are clearly effective in cluster headache. Therefore, the use of at least 100 mg methylprednisone (or equivalent corticosteroid) given orally or at up to 500 mg i.v. per day over 5 days (then tapering down) is recommended. Methysergide, lithium and topiramate are recommended as alternative treatments. Surgical procedures, although in part promising, require further scientific evaluation. For paroxysmal hemicranias, indomethacin at a daily dose of up to 225 mg is the drug of choice. For treatment of SUNCT syndrome, large series suggest that lamotrigine is the most effective preventive agent, with topiramate and gabapentin also being useful. Intravenous lidocaine may also be helpful as an acute therapy when patients are extremely distressed and disabled by frequent attacks.

Objectives

These guidelines give evidence-based recommendations for the treatment of cluster headache, paroxysmal hemicranias and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome. A brief clinical description of the headache disorders is included. The headache disorders are defined based on the diagnostic criteria of the International Headache Society (IHS) [1].

Background

The second edition of the classification of the IHS provided a new primary headache group named the trigeminal-autonomic cephalalgias (TACs), which involves activation of trigeminovascular nociceptive pathways with reflex cranial autonomic activation [1]. All these headache syndromes have two features in common: short-lasting, unilateral, severe headache attacks and accompanying typical cranial autonomic symptoms. These syndromes differ in duration, frequency and rhythmicity of the attacks, and in the intensity of pain and autonomic symptoms. To date, the following syndromes belong to the TACs:

- episodic and chronic cluster headache
- episodic and chronic paroxysmal hemicrania

Correspondence: Arne May MD, Department of Systems Neuroscience, Universitäts-Krankenhaus Eppendorf (UKE), Martinistr. 52, D-20246 Hamburg, Germany (tel.: 040 42803 9189; fax: 040 42803 9955; e-mail: a.may@uke.uni-hamburg.de).

- SUNCT syndrome.

These syndromes differ in duration, frequency and rhythmicity of the attacks [2], and in the intensity of pain and autonomic symptoms, as well as treatment options (see Table 4). In a series of well-documented case reports presenting three atypical cluster headaches, the author suggests that as more cluster patients are seen by headache specialists, new forms of this well-defined primary headache syndrome will be identified [3]. However, the concept of trigeminal-autonomic syndromes is certainly useful for clinicians seeking a pathophysiological understanding of the primary neurovascular headaches and allowing us to place the various strategies aimed at treating or preventing these headaches into context.

The purpose of this paper was to give evidence-based treatment recommendations for the different TACs. The recommendations are based on scientific evidence from clinical trials and on the expertise of the European Federation of Neurological Societies (EFNS) task force. The legal aspects of drug prescription and drug availability in the different European countries will not be considered. The definitions of the recommendation levels follow the EFNS criteria [4].

Search strategy

A literature search was performed using the reference databases MedLine, Science Citation Index and the Cochrane Library; the keywords used were 'cluster headache', 'paroxysmal hemicrania', 'SUNCT', 'treatment' and 'trial' (last search in January 2006). All papers published in English, German or French were considered if they described a controlled trial or a case series on the treatment of at least five patients (or less in paroxysmal hemicrania or SUNCT syndrome). Papers discovered by this search were reviewed, as were refer-

ences cited therein. In addition, review books [5,6], the German treatment recommendations for cluster headache [7] were consulted and abstracts with new data from the most recent congress of the IHS (Kyoto, October 2005) were hand searched.

Methods for reaching a consensus

All authors performed an independent literature search. All members of the task force read the first draft and discussed changes by email. All recommendations had to be agreed on by all members of the task force unanimously. The background of the research strategy and of reaching consensus and the definitions of the recommendation dosages used in this paper follow the EFNS guidelines [4].

Clinical syndromes

The International Classification of Headache Disorders [1] uses explicit diagnostic criteria (see Tables 1–3). However, no single examination (e.g. imaging) is able to define, ensure or differentiate idiopathic headache syndromes [8]. Nevertheless, in the clinical setting, the use of neuroimaging [cerebral computed tomography, magnetic resonance imaging (MRI), MR-angiography, etc.] for headache patients varies widely. Electrophysiological and laboratory examinations including examination of the cerebrospinal fluid are not helpful. For the initial diagnosis and in the case of an abnormal neurological examination, a cranial computed tomography scan and a cranial MRI should be considered in order to exclude abnormalities of the brain. Particularly in older patients, mass lesions or malformations in the midline have been described to be associated with symptomatic cluster headache [9,10] or in SUNCT where

Table 1 Diagnostic criteria of cluster headache

The International Classification of Headache Disorders [1]

A: At least five headache attacks fulfilling criteria B–D

B: Severe or very severe unilateral orbital, supraorbital and/or temporal headache attacks, which last untreated for 15–180 min. During part (but less than half) of the time course of the cluster headache, attacks may be less severe, less frequent or of shorter or longer duration

C: The headache is accompanied by at least one of the following symptoms ipsilateral to the pain:

1. Conjunctival injection or lacrimation
2. Nasal congestion and/or rhinorrhoea
3. Eyelid oedema
4. Forehead and facial sweating
5. Miosis and/or ptosis
6. A sense of restlessness and agitation

D: The attacks have a frequency from one every other day to 8 per day

E: History or physical and neurological examination do not suggest any other disorder and/or they are ruled out by appropriate investigations

Episodic cluster headache: at least two cluster periods lasting 7 days to 1 year separated by pain-free periods lasting ≥ 1 month

Chronic cluster headache: attacks occur for more than 1 year without remission or with remission < 1 month

Probable cluster headache: attacks fulfilling all but one criteria for cluster headache

Table 2 Diagnostic criteria of paroxysmal hemicrania

-
- A. At least 20 attacks fulfilling criteria B–D
 - B. Attacks of severe unilateral orbital, supraorbital or temporal pain lasting 2–30 min
 - C. Headache is accompanied by at least one of the following:
 1. ipsilateral conjunctival injection and/or lacrimation
 2. ipsilateral nasal congestion and/or rhinorrhoea
 3. ipsilateral eyelid oedema
 4. ipsilateral forehead and facial sweating
 5. ipsilateral miosis and/or ptosis
 - D. Attacks have a frequency above 5 per day for more than half the time, although periods with lower frequency may occur
 - E. Attacks are prevented completely by therapeutic doses of indomethacin
 - F. Not attributed to another disorder
-

Table 3 Diagnostic criteria of SUNCT syndrome

-
- A. At least five attacks fulfilling criteria B–D
 - B. Attacks of unilateral orbital, supraorbital or temporal stabbing or pulsating pain lasting 5–240 s
 - C. Pain is accompanied by ipsilateral conjunctival injection and lacrimation
 - D. Attacks occur with a frequency from 3 to 200 per day
 - E. Not attributed to another disorder
-

lesions involving the posterior fossa or region of the pituitary gland need to be considered [11].

Episodic and chronic cluster headache (IHS 3.1)

The diagnostic criteria of cluster headache are presented in Table 1. Cluster headache is defined as a paroxysmal, strictly unilateral, very severe headache, typically with a maximum of pain focussed in the retroorbital area. The unilateral autonomic symptoms such as ptosis, miosis, lacrimation, conjunctival injection, rhinorrhoea and nasal congestion only present during the pain attack are ipsilateral to the pain, indicating parasympathetic hyperactivity and sympathetic impairment. About 3% of all patients lack autonomic symptoms [12] and, in rare cases, sympathetic disturbances persist on the previously affected side of the face in patients whose cluster headache has switched sides [6]. Another clinical landmark of the syndrome is the circadian rhythmicity of the relatively short-lived (15–180 min) painful attacks. In the episodic form, attacks occur daily for some weeks followed by a period of remission. In the chronic form, attacks occur without significant periods of remission, although again there may be periods of worsening frequency as if there is still an element of seasonal cycling occurring. On average, a cluster period lasts 6–12 weeks whilst remissions can last up to 12 months. Cluster headache is regarded as a biorhythmic disorder because the attacks often occur with

a strong periodicity and because the cluster bouts regularly occur during spring and autumn. Furthermore, changes of the diurnal release of hormones involved in biorhythmicity have been detected. Compared with migraine, cluster headache is relatively uncommon [13–15]. The prevalence of cluster headache is less than 1% [16] and mostly affects men [17] with a male to female ratio between 2.5 to 1 and 7.1 to 1 [18]. In recent years, the number of female patients with cluster headache has increased [19]. It is not clear if this is a genuine change or simply increased recognition [20]. A genetic background for cluster headache has not been described, but is likely [16]. Cluster headache is rarely but certainly seen in children and there is a familial occurrence between 2% and 7%. On average, headaches start between the age of 28 and 30 (but can start at every age). After 15 years, 80% of the cluster headache patients still have attacks [18].

Episodic and chronic paroxysmal hemicrania (IHS 3.2)

Paroxysmal hemicrania was first described in 1974 in its chronic form [21] (for a recent review see Ref. [22]). The paroxysmal headache attacks, the character and localization of the pain, and the autonomic symptoms are very similar to those observed in cluster headache. In contrast to cluster headache, the attacks are shorter (2–30 min) and more frequent (more than 5 attacks per day). The autonomic symptoms are often less severe than in cluster headache. The diagnostic criteria of paroxysmal hemicrania are listed in Table 2. Some patients report that their attacks can be triggered by irritation of the neck, in particular in the cervical segments C2 and C3. There is an episodic and a chronic form of paroxysmal hemicrania. The criteria for this differentiation are the same as in cluster headache (see above). The most important criterion for the diagnosis of paroxysmal hemicrania is the complete response to indomethacin. Within 1 week (often within 3 days) after the initiation of indomethacin at an adequate dosage the attacks disappear and this effect is maintained long-term. The prevalence is very low; exact figures are not known. It is estimated that the paroxysmal hemicranias comprise about 3–6% of all TACs. The headache usually starts between the ages of 20 and 40, although children with a clear indomethacin response have been described [23,24]. In contrast to cluster headache, the male to female ratio is 1:3.

SUNCT syndrome (IHS 3.3)

The name of this syndrome (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) describes its typical clinical features. It

Table 4 Clinical comparison of cluster headache with related headache syndromes

	Cluster headache	Paroxysmal hemicrania	SUNCT syndrome
Epidemiology			
Gender (male:female)	3:1	1:3	8:1
Prevalence	0.9%	0.02%	Very rare
Age of onset	28–30 years	20–40 years	20–50 years
Pain			
Quality	Boring, throbbing	Boring	Stabbing
Intensity	Extremely high	High	Moderate to high
Localization	Periorbital	Orbital, temporal	Orbital, temporal
Duration of attack	15–120 min	2–45 min	5–250 s
Frequency of attack	1–8/day	1–40/day	1/day to 30/h
Autonomic symptoms	++	++	+
Circadian rhythmicity	+	(-)	-
Alcohol trigger	++	(+)	(-)

SUNCT, short-lasting unilateral neuralgiform pain with conjunctival injection and tearing. Modified from Ref. [2]. - = none; (-) = rare; (+) = infrequent; + = modest; ++ = strong.

was first described in 1989 [25] (for a review see Ref. [26]); the diagnostic criteria are listed in Table 3. SUNCT syndrome is characterized by very short (5–240 s) attacks with neuralgiform pain quality and severe intensity. The attacks occur at a frequency of 60 (3–200) per day on average, are strictly unilateral (periorbital), and are often triggered by touching, speaking or chewing. When triggered there is no refractory period. The autonomic symptoms are mostly restricted to lacrimation and conjunctival injection. Distinct episodic and chronic forms of SUNCT syndrome are yet to be recognized in formal classifications, but both types occur. The most important differential diagnosis is the classical trigeminal neuralgia. In trigeminal neuralgia, unlike in SUNCT syndrome, autonomic symptoms are not prominent and triggered attacks have a clear refractory period [27]. SUNCT syndrome is uncommon and its true frequency is unclear. The male to female ratio is 1:4. The diagnosis of SUNCT syndrome follows the same pattern as described for cluster headache.

Treatment of cluster headache

The treatment of cluster headache is based on empirical data rather than on a pathophysiological concept of the disease [20,28,29]. Although the headache attacks are usually excruciating, drug treatment in cluster headache shows a placebo rate similar to that observed in migraine treatment [30], about 30%. In general, cluster headache treatment can be divided into acute therapy aimed at aborting individual attacks and prophylactic therapy aimed at preventing recurrent attacks during the cluster period [11,31,32]. Non-drug treatment is ineffective in nearly all patients (Table 4).

Attack treatment

Inhalation of pure (100%) oxygen via a non-rebreathing facial mask with a flow rate of at least 7 l/min (sometimes more than 10 l/min) is effective for stopping cluster headache attacks [33,34]. The inhalation should be in a sitting, upright position. There are no contraindications known for the application of oxygen (Table 5). It is safe and without side effects. In some patients, oxygen is effective even when the pain is at maximal intensity, whilst in others the attack is delayed for minutes to hours rather than completely aborted. In the latter case, oxygen intake has to be restricted, otherwise the attack frequency may significantly increase [20]. About 60% of all cluster headache patients respond to this treatment with a significant pain reduction within 30 min [35,36]. Although previously much discussed, a recent placebo-controlled, double-blind trial confirmed unambiguously that hyperbaric oxygen is ineffective in preventing cluster headache attacks [37].

In double-blind, placebo-controlled trials, the 5-HT_{1B/D} agonist sumatriptan 6 mg injected subcutaneously is effective in about 75% of all cluster headache patients (i.e. pain free within 20 min) [38–40]. Doses less than 6 mg have also been described to be effective [41]. It is safe with no evidence of tachyphylaxis or rebound in most of the patients, even after frequent use [42–44], although recent evidence suggests that cluster headache patients with migraine may experience rebound headache [45]. Contraindications are cardio- and cerebrovascular disorders and untreated arterial hypertension. The most uncomfortable side effects are chest pain and distal paresthesia [46]. In recent open and double-blind, placebo-controlled trials, sumatriptan nasal spray 20 mg [47,48] and oral zolmitriptan 10 mg [49] were also effective within 30 min. The authors have found

Therapy	Treatment of choice		
	Cluster headache	Paroxysmal hemicrania	SUNCT syndrome
Acute	100% oxygen, 15 l/min (A) Sumatriptan 6 mg s.c. (A) Sumatriptan 20 mg nasal (A) Zolmitriptan 5 mg nasal (A/B) Zolmitriptan 10 mg nasal (A/B) Zolmitriptan 10 mg oral (B) Zolmitriptan 5 mg oral (B) Lidocain intranasal (B) Octreotide (B)	None	None
Preventative	Verapamil (A) Steroids (A) Lithium carbonate (B) Methysergide (B) Topiramate (B) Ergotamin tartrate (B) Valproic acid (C) Melatonin (C) Baclofen (C)	Indomethacin (A) Verapamil (C) NSAIDs (C)	Lamotrigine (C)

For exact doses see text (A denotes effective, B denotes probably effective, C denotes possibly effective).

5 mg zolmitriptan nasal spray to be highly effective and a well designed study has just been completed [50]. The preemptive use of 5-HT_{1B/D} agonists (triptans) for cluster headache remains controversial. Oral sumatriptan 100 mg given t.i.d. were not effective in preventing cluster headache attacks in a placebo-controlled trial [51]. In open trials, 40 mg eletriptan per day [52] or 2.5–5 mg naratriptan per day [53] reduced the number of cluster headache attacks.

Oral ergotamine has been used in the treatment of cluster headache attacks for more than 50 years [54–56] and is effective when given very early in the attack. It has been recommended as an aerosol spray for the treatment of acute cluster headache attacks [57,58]. However, modern trials are missing. The intranasal application of dihydroergotamine in cluster headache attacks was not superior to placebo in a single trial [59]. Very recently, the intravenous application of 1 mg dihydroergotamine over 3 days has been shown to be effective for the abatement of severe cluster attacks in an open retrospective trial [60], and this is our clinical experience for some patients. Ergotamine has also been considered for short-term prophylaxis as ergotamine suppositories need a long time until the onset of efficacy. They have been proposed at a dose of 2 mg for short-term prophylaxis, given in the evening to prevent cluster headache attacks during the night [28,61].

The nasal application of lidocaine (1 ml with a concentration of 4–10% ipsilateral to the pain; the head should be reclined by 45° and rotated to the affected side by 30–40°) is effective in at least one-third of the patients [62–64]. It is thought to block the pterygo-

palatine (sphenopalatine) fossa region. The use of lidocaine evolved from early observations that cocaine is effective in aborting acute cluster headache attacks, although it is difficult to determine whether the clinical usefulness of cocaine in aborting acute cluster headache attacks [65] is due to its anaesthetic or euphoric properties.

Very recently, 100 µg subcutaneous octreotide has been shown to be effective in the treatment of acute cluster headache attacks in a double-blind, placebo-controlled trial [66], confirming previous observations on the efficacy of parenteral somatostatin in cluster headache [67].

Preventive drug treatment

The importance of an effective preventive regimen cannot be overstated. As many patients have between one and eight short-lived attacks a day, repeated attempts at abortive therapy may result in overmedication or toxicity. The primary goal of preventive therapy is to produce a suppression of attacks and to maintain remission over the expected duration of the cluster period.

Verapamil at a daily dosage of 240–960 mg has been established as the drug of first choice in the prophylaxis of episodic and chronic cluster headache [11,68], although only a few double-blind, placebo-controlled trials are available. Controlled trials comparing verapamil and lithium with placebo showed an efficacy of both substances, with a more rapid onset of action for verapamil [69]. The comparison of verapamil

Table 5 Treatment recommendations for cluster headache, paroxysmal hemicrania and SUNCT syndrome

360 mg against placebo also showed the superiority of verapamil [70]. In some cases, a daily dose of more than 720 mg may be necessary [11,71]. Regular echocardiographic (ECG) controls are required to control for an increase in cardiac conduction time reflected in a prolongation of the PR interval [72]. Sometimes, ECG may be necessary because of the negative inotropic effects of verapamil. Side effects of verapamil are bradycardia, ankle oedema, constipation, gastrointestinal discomfort, gingival hyperplasia [73] and dull headache. However, it is generally well tolerated and can be used safely in conjunction with sumatriptan, ergotamine, corticosteroids and other preventive substances. There is no evidence for an optimal dosage of verapamil. An increase of 80 mg every 14 days is recommended. The full efficacy of verapamil can be expected within 2–3 weeks. Both the regular- and extended-release preparations have been shown to be useful, but no direct comparative trials are available. In the first 2 weeks of verapamil administration, corticosteroids are also administered by some clinicians.

There are no adequate randomized, placebo-controlled trials available for the use of corticosteroids in cluster headache. Several open studies and case series have been published and reviewed by Ekbom and Hardebo [19]. All of the open studies confirmed the clinically well known efficacy of steroids given under different regimens (30 mg prednisone/day and higher; 2 × 4 mg dexamethasone per day). They are a very effective initial prophylactic option, rapidly suppressing attacks during the time required for the longer-acting preventive agents to take effect. However, some patients are attack-free only with steroids and consequently continuous administration of steroids is necessary. As with verapamil, no evidence for the best regime of steroid administration exists. At the beginning of steroid treatment, 60–100 mg of prednisone given once a day for at least 5 days is recommended, then decreasing the dosage by 10 mg every day. About 70–80% of all cluster headache patients respond to steroids. Intravenous and oral application of steroids can also be successfully combined [74].

Lithium (lithium carbonate) has been studied in cluster headache prophylaxis at a daily dosage between 600 and 1500 mg in more than 20 open trials reviewed by Ekbom [75]. The improvement in chronic cluster headache was reported to be as high as 78% (63% in episodic cluster headache). A recent placebo-controlled trial, however, did not reproduce the beneficial effect of lithium in episodic cluster headache [76]. Yet, in a comparative, double-blind crossover study, lithium and verapamil showed similar efficacy (with a more rapid improvement under verapamil) and tolerability was better under verapamil [69]. The plasma level should be

monitored and kept between 0.6 and 1.2 mmol/l [77]. Regular control of liver, renal and thyroid function and of electrolytes is required. Major side effects are hyperthyreosis, tremor and renal dysfunction. As lithium in general has a narrow therapeutic window, it is particularly recommended for chronic cluster headache when other drugs are ineffective or contraindicated.

Methysergide has been recommended for episodic cluster headache [19,20,78,79]. However, no placebo-controlled, double-blind studies are available. The efficacy rates reported in open studies were reviewed by Ekbom [5]. The number of patients responding positively to methysergide ranged between 20% and 73%; it was more effective in episodic cluster headache. The doses applied in the open studies varied from 4 to 16 mg. Usually, methysergide is administered at a daily dose of 4–8 mg and can be increased up to 12 mg (starting with 1 mg/day). Methysergide should be used with caution when patients are receiving other ergotamine derivatives or triptans. As there is a definite incidence of pulmonary and retroperitoneal fibrosis under long-term use, the continuous use of methysergide is limited to 6 months [80,81].

The antiserotonergic drug pizotifen (3 mg/day) has been shown to be effective in cluster headache prophylaxis in a single-blind, placebo-controlled older trial [82]. However, on the basis of a review of seven small studies [83], one must conclude that pizotifen has only a modest effect. Its use is limited by side effects such as tiredness and weight gain. Valproic acid has been studied in two open trials with acceptable results [84,85] and in one controlled study in which it did not differ from placebo [86]. These trials suggest that valproic acid is generally ineffective in cluster headache, but can be tried as drug of third choice at a daily dose between 5 and 20 mg/kg body weight. Open studies suggest that topiramate is effective in the prophylaxis of cluster headache [87–90]. The recommended dose is at least 100 mg/day, with a starting dose of 25 mg. Main side effects are cognitive disturbances, paresthesias and weight loss. It is contraindicated in nephrolithiasis. For the ipsilateral intranasal application of capsaicin, two open [91,92] and one double-blind, placebo-controlled [93] trials have been published showing an efficacy in about two-third of the patients after repeated application. Intranasal application of civamide showed modest efficacy in a recent double-blind, placebo-controlled study [94]. Although such studies claim to be blind, this is hard to accomplish, given the irritating nature of the nasally applied drug treatment.

Ten milligrams of oral melatonin was effective in a double-blind, placebo-controlled study [95]. In otherwise refractory cluster headache, however, melatonin did not produce any additional efficacy [96]. There is no

evidence that baclofen 15–30 mg [97], botulinum toxin [98] or transdermal clonidine [99] have any prophylactic effect in cluster headache. Although there is no valid evidence for the superiority of combining various prophylactic drug treatments in cluster headache, it is important to realize that some patients may do better with a combination rather than with extensively high doses of a single therapy [20]. In clinical practice, a combination of drugs is often required, generally using verapamil at moderate doses (240–480 mg) as the standard medication and any of the above-mentioned prophylactic medications as add-on therapy. Based on a consensus obtained at the 9th International Headache research seminar, some combinations of drugs have been recommended in patients otherwise refractory to single preventative treatments [100].

Interventional and surgical treatment

It has been observed that greater occipital nerve blockade resulted in a significant reduction of cluster headache attacks in about two-thirds of patients [101,102]. This finding confirmed previous observations, but needs to be replicated in controlled trials. Also, suboccipital injection of long-acting steroids was shown to be effective in the prophylaxis of cluster headache in a double-blind, placebo-controlled trial [103,104]. If all drug treatment procedures are ineffective and a secondary cluster headache has been excluded, surgical treatment can be discussed with the patient. Surgical procedures should be considered with great caution because no reliable long-term data are available and because they can induce trigeminal neuralgia or anaesthesia dolorosa. Different methods have been suggested to prevent cluster headache: application of glycerol or local anaesthetics into the cisterna trigeminalis of the Gasserian ganglion [105]; radiofrequency rhizotomy of the Gasserian ganglion [106] or of the trigeminal nerve [107]; microvascular decompression [108]; resection or blockade of the N. petrosus superficialis [109] or of the pterygopalatine ganglion [110]. However, there are also case reports of the complete inefficacy of surgical treatment in cluster headache and related syndromes [111–114]. In some cases, blockade of the greater occipital nerve was effective and may be tried before any other surgical procedure [101,102]. In general, it has to be said that any surgical procedure on peripheral trigeminal structures in episodic cluster headache has to be judged with great caution, as the natural course of the disease includes remission. On the other hand, in chronic cluster headache, there is strong evidence that even a complete trigeminal denervation is not effective in preventing headache attacks or autonomic symptoms [111]. Very

recently, deep brain stimulation of the posterior inferior hypothalamus [115,116] has been shown to be effective in the majority of a sample of patients with intractable cluster headache [117–119]. Recommendations for the selection of patients for this procedure have recently been published [120].

Recommendations

Level A recommendation

The first option for the treatment of acute attacks of cluster headache should be the inhalation of 100% oxygen with at least 7 l/min over 15 min (class II trials) or with the subcutaneous injection of 6 mg sumatriptan (class I trials). An alternative would be sumatriptan 20 mg nasal spray or zolmitriptan 5 mg nasal spray (one class I trial each), with the disadvantage of a slower onset and the advantage of being able to treat more attacks in 24 h than with injected sumatriptan.

Prophylaxis of cluster headache should be tried first with verapamil at a daily dose of at least 240 mg (maximum dose depends on efficacy or tolerability, ECG controls are obligatory with increasing doses). Although no class I or II trials are available, steroids are clearly effective for treating cluster headache. Therefore, the use of at least 100 mg methylprednisone (or equivalent corticosteroid) given orally or up to 500 mg i.v. per day over 5 days (then tapering down) is recommended.

Level B recommendation

Intranasal lidocaine (4%) and subcutaneous octreotide (100 µg) can be tried for treating acute cluster headache attacks if level A medication is ineffective or contraindicated. Oral administration of zolmitriptan at 5–10 mg is effective in some patients (class I trial) but high doses produce more side effects and limit practical use.

Methysergide and lithium are drugs of second choice if verapamil is ineffective or contraindicated. Corticosteroids can be used for short periods where bouts are short or to help establish another medication. Topiramate is promising, but only open trials exist at this point. Melatonin is useful in some patients. Except for lithium, the maximum dose depends on efficacy and tolerability. Ergotamine tartrate is recommended for short-term prophylaxis (class III studies). Despite positive class II studies, pizotifen and intranasal capsaicin should only be used in rare cases because of side effects.

Level C recommendation

Baclofen 15–30 mg and valproic acid showed possible efficacy and can be tried as drugs of third choice.

Surgical procedures are not indicated in most of the patients with cluster headache. Patients with

intractable chronic cluster headache should be referred to centres with expertise in both destructive and neuromodulatory procedures to be offered all reasonable alternatives before a definitive procedure is conducted. Thus, recommendation is regarded as a good practice point.

Treatment of paroxysmal hemicrania

By definition, indomethacin at a daily dose of up to 225 mg is completely effective [121–124]. Indomethacin is clearly superior to placebo in patients with typical paroxysmal hemicranias [125]. Indomethacin should be administered in three or more doses per day because of its short half life of 4 h. Many patients need a high dose of indomethacin only during the first weeks of treatment and then a lower dose can be tried. Very rarely, doses higher than 200 mg/day are required. A proton pump inhibitor should be given in addition as gastrointestinal discomfort and bleeding are the major side effects. Intramuscular indomethacin 50 mg should result in freedom from attacks within 30 min.

There is no drug of similar efficacy as indomethacin for the treatment of paroxysmal hemicrania. However, open studies (class IV) suggest a moderate efficacy of alternative drugs if indomethacin is not tolerated. The best alternative found in these open studies was verapamil [124,126]. Fewer positive reports have been published for acetazolamide [127] and the non-steroidal anti-inflammatory drugs (NSAIDs) piroxicam [128] and acetylsalicylic acid [21,124]. Subcutaneous sumatriptan is ineffective [129]. Limited reports of good effects with the coxibs were rendered unhelpful by safety concerns with long-term use [130,131]. Anaesthetic blockades of pericranial nerves [132] are said to be ineffective although a member of the panel of experts has seen excellent responses to greater occipital nerve blockade [133].

In summary, paroxysmal hemicrania is to be treated with indomethacin up to 200 mg (level A recommendation). Alternatively, verapamil and other NSAIDs can be tried (level C recommendation).

Treatment of SUNCT syndrome

Until recently, there was no consistently effective treatment known for SUNCT syndrome including high doses of indomethacin and anaesthetic blockades [134]. No controlled trials have been published, and the rareness of the syndrome makes this a difficult task. However, some case reports have been published for some drugs, and recent very large series of 52 patients from one centre characterized the syndrome; and its

treatment [135]. Because of the extreme burden caused by this disorder, all reasonable treatment options should be tried.

Amongst all drugs tried for SUNCT syndrome, lamotrigine is the most effective [136] and this is consistent with the previous case reports [26,134,137,138]. Other treatment options include gabapentin [139,140], topiramate [141], intravenous lidocaine [142] and intravenous phenytoin [143]. In some instances these drugs were applied in combination.

In summary, recent large case series outcomes suggest that lamotrigine is the treatment of choice in SUNCT, followed by topiramate and gabapentin.

Need of update

These recommendations should be updated within 3 years, in particular with respect to the efficacy of the newer antiepileptic drugs in the prophylactic treatment of cluster headache and with respect to the efficacy, tolerability and long-term results of the hypothalamic stimulation.

Conflicts of interest

The present guidelines were developed without external financial support. None of the authors declares a conflict of interests. The authors report the following financial supports:

Arne May: Salary from the University Hospital of Hamburg; honoraries and research grants by Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, GlaxoSmithKline, Janssen Cilag, MSD, Pfizer.

Massimo Leone: Salary from the Istituto Nazionale Neurologico C. Besta; honoraries by GlaxoSmithKline, Almirall, Medtronic.

Judit Áfra: Salary by the Hungarian Ministry of Health; honoraries by GlaxoSmithKline.

Mattias Linde: Salary from the Swedish government; honoraries by AstraZeneca, GlaxoSmithKline, MSD, Nycomed, Pfizer.

Peter S. Sándor: Salary from the University Hospital of Zurich; honoraries by AstraZeneca, GlaxoSmithKline, Janssen Cilag, Pfizer, Pharm Allergan.

Stefan Evers: Salary from the government of the State Northrhine-Westphalia; honoraries and research grants by Almirall, AstraZeneca, Berlin Chemie, Boehringer, GlaxoSmithKline, Ipsen Pharma, Janssen Cilag, MSD, Pfizer, Novartis, Pharm Allergan, Pierre Fabre.

Peter J. Goadsby: Salary from the University College of London; honoraries by Almirall, AstraZeneca, GlaxoSmithKline, MSD, Pfizer, Medtronic, Advanced Bionics.

References

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 2nd edition. *Cephalalgia* 2004; **24**(Suppl. 1): 1–160.
2. Goadsby PJ, Lipton RB. A review of paroxysmal hemiplegias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. *Brain* 1997; **120**: 193–209.
3. Rozen TD. Atypical presentations of cluster headache. *Cephalalgia* 2002; **22**: 725–729.
4. Brainin M, Barnes M, Baron JC, *et al.* Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *European Journal of Neurology* 2004; **11**: 577–581.
5. Olesen J, Tfelt-Hansen P, Welch K. *The Headaches*, 2nd edn. Philadelphia: Lippincott Williams & Wilkins, 1999.
6. Sjaastad O (ed.). *Cluster Headache Syndrome*. London: W B Saunders Company Ltd, 1992.
7. May A, Evers S, Straube A, Pfaffenrath V, Diener H. Therapie und Prophylaxe von Cluster Kopfschmerzen und anderen Trigemino-Autonomem Kopfschmerzen. Überarbeitete Empfehlungen der Deutschen Migräne- und Kopfschmerzgesellschaft. *Nervenheilkunde* 2004; **23**: 478–490.
8. Sandrini G, Friberg L, Janig W, *et al.* Neurophysiological tests and neuroimaging procedures in non-acute headache: guidelines and recommendations. *European Journal of Neurology* 2004; **11**: 217–224.
9. Hannerz J. A case of parasellar meningioma mimicking cluster headache. *Cephalalgia* 1989; **9**: 265–269.
10. Purdy RA, Kirby S. Headaches and brain tumors. *Neurologic Clinics* 2004; **22**: 39–53.
11. Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalalgias and hemicrania continua. *Drugs* 2003; **63**: 1637–1677.
12. Ekbom K. Evaluation of clinical criteria for cluster headache with special reference to the classification of the International Headache Society. *Cephalalgia* 1990; **10**: 195–197.
13. D'Alessandro R, Gamberini G, Benassi G, Morganti G, Cortelli P, Lugaesi E. Cluster headache in the Republic of San Marino. *Cephalalgia* 1986; **6**: 159–162.
14. Ekbom K, Ahlborg B, Schele R. Prevalence of migraine and cluster headache in Swedish men of 18. *Headache* 1978; **18**: 9–19.
15. Kudrow L. *Cluster Headache, Mechanism and Management*, 1st edn. New York: Oxford University Press, 1980.
16. Russell MB. Epidemiology and genetics of cluster headache. *Lancet Neurology* 2004; **3**: 279–283.
17. Sjaastad O, Bakketeig LS. Cluster headache prevalence. Vaga study of headache epidemiology. *Cephalalgia* 2003; **23**: 528–533.
18. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology* 2002; **58**: 354–361.
19. Ekbom K, Hardebo JE. Cluster headache: aetiology, diagnosis and management. *Drugs* 2002; **62**: 61–69.
20. May A. Cluster headache: pathogenesis, diagnosis, and management. *Lancet* 2005; **366**: 843–855.
21. Sjaastad O, Dale I. Evidence for a new (?), treatable headache entity. *Headache* 1974; **14**: 105–108.
22. Dodick DW. Indomethacin-responsive headache syndromes. *Current Pain and Headache Reports* 2004; **8**: 19–26.
23. Broeske D, Lenn N, Cantos E. Chronic paroxysmal hemicrania in a young child: possible relation to ipsilateral occipital infarction. *Journal of Child Neurology* 1993; **8**: 235–236.
24. De Almeida D, Cunali P, Santos H, Brioschi M, Prandini M. Chronic paroxysmal hemicrania in early childhood: case report. *Cephalalgia* 2004; **24**: 608–609.
25. Sjaastad O, Saunte C, Salvesen R, *et al.* Shortlasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, sweating, and rhinorrhea. *Cephalalgia* 1989; **9**: 147–156.
26. Matharu MS, Cohen AS, Boes CJ, Goadsby PJ. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome: a review. *Current Pain and Headache Reports* 2003; **7**: 308–318.
27. Goadsby PJ, Matharu MS, Boes CJ. SUNCT syndrome or trigeminal neuralgia with lacrimation. *Cephalalgia* 2001; **21**: 82–83.
28. Dodick D, Rozen T, Goadsby P, Silberstein S. Cluster headache. *Cephalalgia* 2000; **20**: 787–803.
29. Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalalgia. *Lancet Neurology* 2002; **1**: 251–257.
30. Nilsson Remahl AI, Laudon Meyer E, Cordonnier C, Goadsby PJ. Placebo response in cluster headache trials: a review. *Cephalalgia* 2003; **23**: 504–510.
31. May A, Leone M. Update on cluster headache. *Current Opinion in Neurology* 2003; **16**: 333–340.
32. Leone M. Chronic cluster headache: new and emerging treatment options. *Current Pain and Headache Reports* 2004; **8**: 347–352.
33. Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache* 1981; **21**: 1–4.
34. Fogan L. Treatment of cluster headache. A double-blind comparison of oxygen v air inhalation. *Archives of Neurology* 1985; **42**: 362–363.
35. Ekbom K. Treatment of cluster headache: clinical trials, design and results. *Cephalalgia* 1995; **15**: 33–36.
36. Gallagher RM, Mueller L, Ciervo CA. Analgesic use in cluster headache. *Headache* 1996; **36**: 105–107.
37. Nilsson Remahl AI, Ansjon R, Lind F, Waldenlind E. Hyperbaric oxygen treatment of active cluster headache: a double-blind placebo-controlled cross-over study. *Cephalalgia* 2002; **22**: 730–739.
38. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *New England Journal of Medicine* 1991; **325**: 322–326.
39. Ekbom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. *Acta Neurologica Scandinavica* 1993; **88**: 63–69.
40. Stovner LJ, Sjaastad O. Treatment of cluster headache and its variants. *Current Opinion in Neurology* 1995; **8**: 243–247.
41. Gregor N, Schlesiger C, Akova-Ozturk E, Kraemer C, Husstedt IW, Evers S. Treatment of cluster headache attacks with less than 6 mg subcutaneous sumatriptan. *Headache* 2005; **45**: 1069–1072.
42. Wilkinson M, Pfaffenrath V, Schoenen J, Diener HC, Steiner TJ. Migraine and cluster headache – their

- management with sumatriptan: a critical review of the current clinical experience. *Cephalalgia* 1995; **15**: 337–357.
43. Ekbom K, Krabbe A, Micelli G, *et al.* Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). Sumatriptan Cluster Headache Long-term Study Group. *Cephalalgia* 1995; **15**: 230–236.
 44. Göbel H, Lindner V, Heinze A, Ribbat M, Deuschl G. Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. *Neurology* 1998; **51**: 908–911.
 45. Paemeleire K, Bahra A, Evers S, Matharu M, Goadsby P. Medication-overuse headache in cluster headache patients. *Neurology* 2006; **67**: 109–113.
 46. Dodick DW, Martin VT, Smith T, Silberstein S. Cardiovascular tolerability and safety of triptans: a review of clinical data. *Headache* 2004; **44**(Suppl. 1): S20–S30.
 47. Schuh-Hofer S, Reuter U, Kinze S, Einhaupl KM, Arnold G. Treatment of acute cluster headache with 20 mg sumatriptan nasal spray – an open pilot study. *Journal of Neurology* 2002; **249**: 94–99.
 48. Van Vliet JA, Bahra A, Martin V, *et al.* Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study. *Neurology* 2003; **60**: 630–633.
 49. Bahra A, Gawel MJ, Hardebo JE, Millson D, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; **54**: 1832–1839.
 50. Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby P. Zolmitriptan nasal spray is effective in the acute treatment of cluster headache: a double-blind placebo-controlled crossover study. *Cephalalgia* 2005; **25**: 921.
 51. Monstad I, Krabbe A, Micieli G, *et al.* Preemptive oral treatment with sumatriptan during a cluster period. *Headache* 1995; **35**: 607–613.
 52. Zebenholzer K, Wober C, Vigl M, Wessely P. Eletriptan for the short-term prophylaxis of cluster headache. *Headache* 2004; **44**: 361–364.
 53. Mulder LJ, Spierings EL. Naratriptan in the preventive treatment of cluster headache. *Cephalalgia* 2002; **22**: 815–817.
 54. Horton B, Ryan R, Reynolds J. Clinical observations of the use of E.C. 110, a new agent for the treatment of headache. *Mayo Clinic Proceedings* 1948; **23**: 104–108.
 55. Kunkle EC, Pfeiffer J, Wilhoit WM, Hamrick J. Recurrent brief headache in cluster pattern. *Transactions of the American Neurological Association* 1952; **27**: 240–243.
 56. Friedman AP, Mikropoulos HE. Cluster headaches. *Neurology* 1958; **8**: 653–663.
 57. Graham JR, Malvea BP, Gramm HF. Aerosol ergotamine tartrate for migraine and Horton's syndrome. *New England Journal of Medicine* 1960; **263**: 802–804.
 58. Ekbom K, Krabbe AE, Paalzow G, Paalzow L, Tfelt-Hansen P, Waldenlind E. Optimal routes of administration of ergotamine tartrate in cluster headache patients. A pharmacokinetic study. *Cephalalgia* 1983; **3**: 15–20.
 59. Andersson PG, Jespersen LT. Dihydroergotamine nasal spray in the treatment of attacks of cluster headache. A double-blind trial vs. placebo. *Cephalalgia* 1986; **6**: 51–54.
 60. Magnoux E, Zlotnik G. Outpatient intravenous dihydroergotamine for refractory cluster headache. *Headache* 2004; **44**: 249–255.
 61. Ekbom K. Ergotamine tartrate orally in Horton's histaminic cephalalgia (also called Harris's ciliary neuralgia). *Acta Psychiatrica Scandinavica* 1947; **46**: 106.
 62. Robbins L. Intranasal lidocaine for cluster headache [see comments]. *Headache* 1995; **35**: 83–84.
 63. Mills TM, Scoggin JA. Intranasal lidocaine for migraine and cluster headaches. *Annals of Pharmacotherapy* 1997; **31**: 914–915.
 64. Markley HG. Topical agents in the treatment of cluster headache. *Current Pain and Headache Reports* 2003; **7**: 139–143.
 65. Costa A, Pucci E, Antonaci F, *et al.* The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. *Cephalalgia* 2000; **20**: 85–91.
 66. Matharu MS, Levy MJ, Meeran K, Goadsby PJ. Subcutaneous octreotide in cluster headache: Randomized placebo-controlled double-blind crossover study. *Annals of Neurology* 2004; **56**: 488–494.
 67. Sicuteri F, Geppetti P, Marabini S, Lembeck F. Pain relief by somatostatin in attacks of cluster headache. *Pain* 1984; **18**: 359–365.
 68. May A. Headaches with (ipsilateral) autonomic symptoms. *Journal of Neurology* 2003; **250**: 1273–1278.
 69. Bussone G, Leone M, Peccarisi C, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30**: 411–417.
 70. Leone M, D'Amico D, Frediani F, *et al.* Verapamil in the prophylaxis of episodic cluster headache: a double-blind study vs. placebo. *Neurology* 2000; **54**: 1382–1385.
 71. Gabai IJ, Spierings EL. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989; **29**: 167–168.
 72. Cohen A, Matharu M, Goadsby P. ECG abnormalities on verapamil in cluster headache. *Cephalalgia* 2005; **25**: 1200.
 73. Matharu MS, van Vliet JA, Ferrari MD, Goadsby PJ. Verapamil induced gingival enlargement in cluster headache. *Journal of Neurology, Neurosurgery and Psychiatry* 2005; **76**: 124–127.
 74. Mir P, Alberca R, Navarro A, *et al.* Prophylactic treatment of episodic cluster headache with intravenous bolus of methylprednisolone. *Neurological Science* 2003; **24**: 318–321.
 75. Ekbom K. Lithium for cluster headache: review of the literature and preliminary results of long-term treatment. *Headache* 1981; **21**: 132–139.
 76. Steiner TJ, Hering R, Couturier EGM, Davies PTG, Whitmarsh TE. Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* 1997; **17**: 673–675.
 77. Manzoni GC, Bono G, Lanfranchi M, Micieli G, Terzano MG, Nappi G. Lithium carbonate in cluster headache: assessment of its short- and long-term therapeutic efficacy. *Cephalalgia* 1983; **3**: 109–114.
 78. Curran D, Hinterberger H, Lance J. Methysergide. *Research and Clinical Studies in Headache* 1967; **1**: 74–122.
 79. Dodick DW, Capobianco DJ. Treatment and management of cluster headache. *Current Pain and Headache Reports* 2001; **5**: 83–91.
 80. Graham J, Suby H, LeCompte P, Sadowsky N. Fibrotic disorders associated with methysergide therapy for headache. *New England Journal of Medicine* 1966; **270**: 67–72.
 81. Muller R, Weller P, Chemaissani A. Pleural fibrosis as a side effect of years-long methysergide therapy. *Deutsche Medizinische Wochenschrift* 1991; **116**: 1433–1436.

82. Ekblom K. Prophylactic treatment of cluster headache with a new serotonin antagonist, BC 105. *Acta Neurologica Scandinavica* 1969; **45**: 601–610.
83. Speight TM, Avery GS. Pizotifen (BC-105): a review of its pharmacological properties and its therapeutic efficacy in vascular headaches. *Drugs* 1972; **3**: 159–203.
84. Gallagher RM, Mueller LL, Freitag FG. Divalproex sodium in the treatment of migraine and cluster headaches. *Journal of the American Osteopathic Association* 2002; **102**: 92–94.
85. Hering R, Kuritzky A. Sodium valproate in the treatment of cluster headache: an open clinical trial. *Cephalalgia* 1989; **9**: 195–198.
86. El Amrani M, Massiou H, Bousser MG. A negative trial of sodium valproate in cluster headache: methodological issues. *Cephalalgia* 2002; **22**: 205–208.
87. McGeeney BE. Topiramate in the treatment of cluster headache. *Current Pain and Headache Reports* 2003; **7**: 135–138.
88. Forderreuther S, Mayer M, Straube A. Treatment of cluster headache with topiramate: effects and side-effects in five patients. *Cephalalgia* 2002; **22**: 186–189.
89. Rozen TD. Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia. *Headache* 2001; **41**(Suppl. 1): 25–33.
90. Leone M, Dodick D, Rigamonti A, *et al.* Topiramate in cluster headache prophylaxis: an open trial. *Cephalalgia* 2003; **23**: 1001–1002.
91. Sicuteri F, Fusco BM, Marabini S, *et al.* Beneficial effect of capsaicin application to the nasal mucosa in cluster headache. *Clinical Journal of Pain* 1989; **5**: 49–53.
92. Fusco BM, Marabini S, Maggi CA, Fiore G, Geppetti P. Preventative effect of repeated nasal applications of capsaicin in cluster headache. *Pain* 1994; **59**: 321–325.
93. Marks DR, Rapoport A, Padla D, *et al.* A double-blind placebo-controlled trial of intranasal capsaicin for cluster headache. *Cephalalgia* 1993; **13**: 114–116.
94. Saper JR, Klapper J, Mathew NT, Rapoport A, Phillips SB, Bernstein JE. Intranasal civamide for the treatment of episodic cluster headaches. *Archives of Neurology* 2002; **59**: 990–994.
95. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. Melatonin vs. placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* 1996; **16**: 494–496.
96. Pringsheim T, Magnoux E, Dobson CF, Hamel E, Aube M. Melatonin as adjunctive therapy in the prophylaxis of cluster headache: a pilot study. *Headache* 2002; **42**: 787–792.
97. Hering-Hanit R, Gadoth N. The use of baclofen in cluster headache. *Current Pain and Headache Reports* 2001; **5**: 79–82.
98. Evers S, Rahmann A, Vollmer-Haase J, Husstedt IW. Treatment of headache with botulinum toxin A – a review according to evidence-based medicine criteria. *Cephalalgia* 2002; **22**: 699–710.
99. Leone M, Attanasio A, Grazi L, *et al.* Transdermal clonidine in the prophylaxis of episodic cluster headache: an open study. *Headache* 1997; **37**: 559–560.
100. Tfelt Hansen P. Prophylactic pharmacotherapy of cluster headache. In: Olesen J, Goadsby P, eds. *Cluster Headache and Related Conditions*. Oxford, New York: Oxford University Press, 1999: 257–263.
101. Anthony M. Arrest of attacks of cluster headache by local steroid injection of the occipital nerve. In: Rose C, ed. *Migraine*. Basel: Karger, 1985: 169–173.
102. Peres MF, Stiles MA, Siow HC, Rozen TD, Young WB, Silberstein SD. Greater occipital nerve blockade for cluster headache. *Cephalalgia* 2002; **22**: 520–522.
103. Ambrosini A, Vandenhede M, Rossi P, *et al.* Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. *Pain* 2005; **118**: 92–96.
104. Magnoux E. Greater occipital nerve blockade for cluster headache. *Cephalalgia* 2004; **24**: 239.
105. Ekblom K, Lindgren L, Nilsson BY, Hardebo JE, Waldenlind E. Retro-Gasserian glycerol injection in the treatment of chronic cluster headache. *Cephalalgia* 1987; **7**: 21–27.
106. Taha JM, Tew JM Jr. Long-term results of radiofrequency rhizotomy in the treatment of cluster headache. *Headache* 1995; **35**: 193–196.
107. Ford RG, Ford KT, Swaid S, Young P, Jennelle R. Gamma knife treatment of refractory cluster headache. *Headache* 1998; **38**: 3–9.
108. Lovely TJ, Kotsiakakis X, Jannetta PJ. The surgical management of chronic cluster headache. *Headache* 1998; **38**: 590–594.
109. Onofrio BM, Campbell JK. Surgical treatment of chronic cluster headache. *Mayo Clinic Proceedings* 1986; **61**: 537–544.
110. Sanders M, Zuurmond WW. Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: a 12- to 70-month follow-up evaluation. *Journal of Neurosurgery* 1997; **87**: 876–880.
111. Matharu MS, Goadsby PJ. Persistence of attacks of cluster headache after trigeminal nerve root section. *Brain* 2002; **125**: 976–984.
112. Black D, Dodick DW. Two cases of medically and surgically intractable SUNCT: a reason for caution and an argument for a central mechanism. *Cephalalgia* 2002; **3**: 201–204.
113. Jarrar RG, Black DF, Dodick DW, Davis DH. Outcome of trigeminal nerve section in the treatment of chronic cluster headache. *Neurology* 2003; **60**: 1360–1362.
114. Donnet A, Valade D, Regis J. Gamma knife treatment for refractory cluster headache: prospective open trial. *Journal of Neurology, Neurosurgery and Psychiatry* 2005; **76**: 218–221.
115. Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. *New England Journal of Medicine* 2001; **345**: 1428–1429.
116. Franzini A, Ferrolli P, Leone M, Broggi G. Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. *Neurosurgery* 2003; **52**: 1095–1101.
117. Leone M, Franzini A, Broggi G, May A, Bussone G. Long-term follow-up of bilateral hypothalamic stimulation for intractable cluster headache. *Brain* 2004; **127**: 2259–2264.
118. Schoenen J, Di Clemente L, Vandenhede M, *et al.* Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. *Brain* 2005.
119. May A, Leone M, Boecker H, *et al.* Hypothalamic deep brain stimulation in PET. *Journal of Neuroscience* 2006; **26**: 3589–3593.

120. Leone M, May A, Franzini A, *et al.* Deep brain stimulation for intractable chronic cluster headache: proposals for patient selection. *Cephalalgia* 2004; **24**: 934–937.
121. Sjaastad O, Stovner LJ, Stolt Nielsen A, Antonaci F, Fredriksen TA. CPH and hemicrania continua: requirements of high indomethacin dosages – an ominous sign? *Headache* 1995; **35**: 363–367.
122. Sjaastad O, Apfelbaum R, Caskey W, *et al.* Chronic paroxysmal hemicrania (CPH). The clinical manifestations. A review. *Uppsala Journal of Medical Sciences. Supplement* 1980; **31**: 27–33.
123. Boes CJ, Dodick DW. Refining the clinical spectrum of chronic paroxysmal hemicrania: a review of 74 patients. *Headache* 2002; **42**: 699–708.
124. Evers S, Husstedt IW. Alternatives in drug treatment of chronic paroxysmal hemicrania. *Headache* 1996; **36**: 429–432.
125. Matharu MS, Cohen AS, Frackowiak RS, Goadsby PJ. Posterior hypothalamic activation in paroxysmal hemicrania. *Annals of Neurology* 2006; **59**: 535–545.
126. Shabbir N, McAbee G. Adolescent chronic paroxysmal hemicrania responsive to verapamil monotherapy. *Headache* 1994; **34**: 209–210.
127. Warner JS, Wamil AW, McLean MJ. Acetazolamide for the treatment of chronic paroxysmal hemicrania. *Headache* 1994; **34**: 597–599.
128. Sjaastad O, Antonaci F. A piroxicam derivative partly effective in chronic paroxysmal hemicrania and hemicrania continua. *Headache* 1995; **35**: 549–550.
129. Dahlof C. Subcutaneous sumatriptan does not abort attacks of chronic paroxysmal hemicrania (CPH). *Headache* 1993; **33**: 201–202.
130. Lisotto C, Maggioni F, Mainardi F, Zanchin G. Rofecoxib for the treatment of chronic paroxysmal hemicrania. *Cephalalgia* 2003; **23**: 318–320.
131. Mathew N, Kailasam J, Fischer A. Responsiveness to celecoxib in chronic paroxysmal hemicrania. *Neurology* 2000; **55**: 316.
132. Antonaci F, Pareja JA, Caminero AB, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua: anaesthetic blockades of pericranial nerves. *Functional Neurology* 1997; **12**: 11–15.
133. Afridi S, Shields K, Bhola R, Goadsby P. Greater occipital nerve injection in primary headache syndromes – prolonged effects from a single injection. *Pain* 2006; **26**: 126–129.
134. Pareja JA, Caminero AB, Sjaastad O. SUNCT syndrome: diagnosis and treatment. *CNS Drugs* 2002; **16**: 373–383.
135. Cohen A, Matharu M, Goadsby P. Revisiting the International Headache Society Criteria for SUNCT and SUNA: a case series of 52 patients. *Cephalalgia* 2005; **25**: 1194.
136. Cohen A, Matharu M, Goadsby P. Suggested guidelines for treating SUNCT and SUNA. *Cephalalgia* 2005; **25**: 1200.
137. D'Andrea G, Granella F, Cadaldini M. Possible usefulness of lamotrigine in the treatment of SUNCT syndrome. *Neurology* 1999; **53**: 1609.
138. D'Andrea G, Granella F, Ghiotto N, Nappi G. Lamotrigine in the treatment of SUNCT syndrome. *Neurology* 2001; **57**: 1723–1725.
139. Hunt CH, Dodick DW, Bosch EP. SUNCT responsive to gabapentin. *Headache* 2002; **42**: 525–526.
140. Porta-Etessam J, Benito-Leon J, Martinez-Salio A, Berbel A. Gabapentin in the treatment of SUNCT syndrome. *Headache* 2002; **42**: 523–524.
141. Matharu MS, Boes CJ, Goadsby PJ. SUNCT syndrome: prolonged attacks, refractoriness and response to topiramate. *Neurology* 2002; **58**: 1307.
142. Matharu MS, Cohen AS, Goadsby PJ. SUNCT syndrome responsive to intravenous lidocaine. *Cephalalgia* 2004; **24**: 985–992.
143. Schwaag S, Frese A, Husstedt IW, Evers S. SUNCT syndrome: the first German case series. *Cephalalgia* 2003; **23**: 398–400.