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EFNS TASK FORCE ARTICLE

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

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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].

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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

• 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 references 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. ipisilateral 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

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

	Treatment of choice		
Therapy	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 pterygopalatine (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

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 paroxymal 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

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